A systematised review of assisted standing for persons in a prolonged disorder of consciousness

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A systematised review of assisted standing for persons in a prolonged disorder of consciousness

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Certificate of Ethical Approval

Applicant:

Harriet Ng

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A systematic review of assisted standing with or without passive leg movements for persons in a prolonged disorder of consciousness.

This is to certify that the above named applicant has completed the Coventry University Ethical Approval process and their project has been confirmed and approved as Low Risk

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Contents

Abstract

Background: Persons in disorders of consciousness after brain injury pose a highly complex philosophical and scientific issue. With medical advances, more people now survive previously fatal brain injuries but can be left in prolonged disorders of consciousness. The mechanisms for regaining consciousness after brain injury are still poorly understood. Treatment to remediate consciousness is an important rehabilitative issue. Passive standing using equipment such as a tilt table is a therapeutic method used with the intention to aid the recovery of consciousness. This is a commonly used treatment method but, it is not known if it is effective.

Research objective: The intention of this systematised review is to analyse the evidence for passive standing's effect on consciousness for those in a prolonged disorder of consciousness.

Methods: This review followed a PRISMA-P protocol for comprehensive reporting. The use of this ensured structured searching, selection and presentation of articles. The search was completed independently by two separate researchers. The search strategy was created to retrieve all possible causes of disorders of consciousness, combined with all conceivable passive standing devices and assessments of consciousness. Papers were identified through primary database searching (in Medline, CINAHL, AMED, PEDro and The Cochrane Library) and post-citation searching (via Scopus). A search for relevant grey literature was performed in profession-specific magazines, theses, conference proceedings and clinical trial registries. Inclusion criteria were any papers that evaluated passive standing on adults who were in defined disorders of consciousness. Exclusion criteria included active stand studies, paediatric studies and animal studies, as these are inappropriate to answer the research question. A consensus was reached through discussion between the two separate researchers.

Results: Ten papers were appropriate for inclusion through adherence to the inclusion and exclusion criteria. Data collection from the papers was completed using the Cochrane data collection form (2014). For all articles assessment of study quality and bias was completed using the Cochrane risk of bias tool (2014), additionally, the Downs and Black tool (1998) was used to assess the quality of observational studies. The majority of studies reviewed were of low to medium quality. The results of these did not provide conclusive recommendations as to the effectiveness of supportive standing. This

systematised review has created recommendations for future research to assess if standing is a therapeutically effective treatment of consciousness.

Chapter 1: Introduction

Assisted standing is commonly used to increase arousal and alertness for people in prolonged disorders of consciousness. The treatment uses an assisted standing device to fully support a person to stand and is commonly used in both acute and rehabilitation settings (Moore and Jones 2011; Chang et al. 2004). However, there is limited evidence to support standing treatments' ability to increase consciousness and no systematic review of its efficacy. The objective is to assess the effect of single standing or standing regimes ability to treat consciousness, through a systematised review of the literature. This introduction will address the global context of brain injury, previous reviews on standing regimes and the need for effective treatment. The definitions of disorders of consciousness and other terminology will be described in the literature background. A glossary of acronyms is in appendix 1.0.

Improvements in acute medical treatment mean that today many more people survive severe brain injury, through either traumatic or non-traumatic causes (Steppacher, Kaps and Kissler 2014: 401). This creates an increasing number of people in disorders of consciousness and the need to care for and rehabilitate these individuals. Approximately 10% of traumatic brain injuries ("TBIs") are severe enough to cause a disorder of consciousness (Corrigan, Selassie and Orman 2010: 72). However, such data are not as widely available for those with severe non-traumatic brain injuries. Previous research has shown that approximately 10% of stroke patients undergo mechanical ventilation (Mayer et al. 2000: 2348), due to decreased levels of consciousness (Diedler et al. 2009: 365). Improved medical care after non-traumatic injuries also means that many who would not have survived such injuries now do so (Kitzinger and Kitzinger 2013: 1096). It is essential for health care providers to give effective rehabilitation to the increasing numbers of people in prolonged disorders of consciousness ("PDOC").

Increased prevalence in brain injury has been calculated through several meta-analyses (Tagliaferri et al. 2006; Peeters et al. 2015). Tagliaferri et al. (2006: 265) found that the mean incidence rate of

hospitalisation with TBI for Europe was approximately 235 per 100,000 population between 1980 and 2003. A subsequent meta-analysis by Peeters et al. (2015: 1692) found the average incidence to be 326 per 100,000 population per year between 1990-2014. However, this increase could be accounted for by Peeters et al. (2015) using a random effect meta-analysis due to the variability of the individual studies, whereas the heterogeneity of the data was not accounted for in the Tagliaferri et al. (2006) study. The reported cause of increasing levels of brain injury worldwide is from motor-vehicle accidents in middle and low-income countries (Maas 2008: 728). Indeed, the World Health Organisation forecasts that by 2020, TBI and road traffic accidents will be the third greatest cause of disease and injury worldwide (Tabish and Syed 2015: 1). In high-income countries, there is an increase in TBI as a result of falls in the growing older population (Maas 2008: 721). Hence, the consequences of brain injuries are a growing and global issue.

With more people surviving previously lethal brain injuries the need for medical and therapeutic care is also increasing. It is essential to ascertain which treatments for consciousness are most effective and economical. The cost of usual care is considerable, but difficult to estimate. Rehabilitation for a person in a vegetative state ("VS") in a regional level hospital has been costed at £193,450 per year (Turner-Stokes 2014: 259), with staffing accounting for two-thirds of costs (Turner-Stokes 2014: 261). To provide the best care for individuals, it is important to determine the efficacy of treatments for consciousness.

To date, there has been no systematic review assessing the efficacy of a standing regimes ability to increase consciousness. Three previous systematic reviews have looked at the effect of supportive standing on other outcome measures for persons with mixed neurological conditions (Newman and Barker 2012; Paleg and Livingstone 2015; Glickman, Geigle and Paleg 2010). Standing regimes are used to treat multiple therapeutic goals in one session. However, the effect that standing has on each individual outcome has mixed evidential support. Newman and Barker (2012) looked at multiple outcomes including lower limb range of movement, bone mineral density, spasticity and gross motor function. Paleg and Livingstone (2015) and an earlier study by Glickman, Geigle and Paleg (2010) looked at all of these outcome measures, but also included mental function and pain. Consciousness is commonly treated by standing regimes, despite this none of these systematic reviews looked at level

of consciousness as an outcome measure. These three reviews do reflect the multifactorial use of standing treatment and have been important in highlighting the need for more structured assessment of standing protocols.

It is important to briefly explore the previous reviews assessment of standing treatments on outcomes other than consciousness. Previous reviewers found the evidence being limited by a few factors, firstly the heterogeneity of populations from individual studies. Although a diverse patient population reflects clinical practice, it is very difficult to draw generalisable conclusions from a heterogeneous study population. For example, Ben et al. (2005) conducted a study of tilt table standing's effect on ankle mobility. All participants in this study had a spinal cord injury, many had variable muscle tone, and two had flaccid paralysis (Ben et al. 2005: 253). These authors measured ankle range of movement, but the inclusion of persons with flaccid paralysis will have affected the statistical calculation of treatment effect, as the difference between the start and end range of movement will be minimal for these two participants (Ben et al. 2005: 253). Such a heterogeneous population affects the internal validity of the study. This is common-place in primary articles on this subject. The clinical diversity in their included studies prevented focused conclusions being made for effective practice.

The variability of study designs is a secondary flaw identified by previous review authors. Many studies have only analysed a single standing intervention (Maynard, Bakheit and Shaw 2005; Luther et al. 2007), whereas others have looked at standing protocols lasting between two and four weeks (Wong et al. 1997; Adams and Hicks 2011; Baker, Cassidy and Rone-Adams 2007). Paleg and Livingstone (2015) noted that few articles gave replicable specifics on the implementation of standing programmes. Glickman, Geigle and Paleg (2010) agreed that the lack of rigorous methods and variability of outcome measures limited the review's findings. Despite this, Paleg created a mathematical formula to give advice on treatment duration (Paleg and Livingstone 2015). This contradicts the stated limitations of their review, mainly that the majority of studies were of low-quality with small sample sizes creating low strength recommendations (Paleg and Livingstone 2015: 13). Overall the effectiveness of standing treatments for multiple therapeutic outcomes has been

difficult to assess due to the current evidence base. The use of standing regimes to affect consciousness has not yet been reviewed.

A major goal of rehabilitation for those in disorders of consciousness is to increase their arousal and enhance their ability to communicate. Pharmaceutical agents to increase levels of consciousness have a firmer evidence base and more effective use in practice; this will be discussed further in the literature background. Therapeutic standing treatments are also used with the intention of increasing levels of arousal. This has been supported by multiple authors, the highest quality trial coming from Krewer et al. (2015). These authors found greater improvements in consciousness with standard rehabilitation plus additional standing on a tilt table. However, further evidential support is needed to best define if standing protocols can improve consciousness. Hence it is necessary to synthesise the evidence base through a systematised review. (Chang et al. 2004; Moore and Jones 2011)

Standing treatments are commonly used with the intention of increasing a person's level of consciousness (Chang et al. 2004; Moore and Jones 2011). As there has been no systematised review of standing treatments' ability to improve consciousness, there is a danger of providing an ineffective treatment. This goes against the core of evidence-based practice, which it is the intention to integrate expertise derived from practice with research evidence (Sackett et al. 1996: 71). For vulnerable individuals that cannot consent for themselves, it becomes ethically important to use efficacious treatments, in order to ensure the best therapeutic treatment is being given despite the high resources it uses. Dr A. Cochrane defined key concepts to test healthcare interventions, for instance, efficacy which is defined as an intervention that does more harm than good in ideal circumstances (Cochrane 1972: 26-35). However, for the treatment of consciousness with fully supportive standing regimes, there is a wealth of practical experience, but a scarcity of research evidence. This systematised review seeks to collate all current evidence on the efficacy of assisted standing regimes to affect consciousness.

Chapter 2: Literature Background

This literature background addresses the terminology of prolonged disorders of consciousness, prognosis, ethical considerations, assessment of consciousness, treatment of consciousness, the evidence base and pathophysiological mechanisms underpinning standing treatments' ability to increase consciousness.

Severe brain injury results in the suspension of consciousness (Giacino et al. 2014: 99). Consciousness is difficult to define medically, but the best working definition cited by leading authors in the field comes from William James who stated: "normal human consciousness consists of serially time-ordered, organised, restricted and reflective awareness of self and the environment" (1894: 516). Total dissolution of consciousness is defined as a *coma* (Giacino et al. 2014: 100). This is a loss of stimulus-induced or spontaneous arousal and absence of sleep-wake cycles (Plum and Posner 2007: 7). The return of sleep-wake cycles and alertness, but an absence of awareness, is termed as a *vegetative state* ("VS") (Turner-Stokes et al. 2014: 3). Progress from a VS is characterised by reproducible responses above the level of reflexive behaviour which demonstrate awareness of one's own environment, and this is defined as a *minimally conscious state* ("MCS") (Turner-Stokes et al. 2014: 3). An all-encompassing term for these three states is a *prolonged disorder of consciousness* ("PDOC") (Turner-Stokes et al. 2014: 12). These definitions assist in the characterisation and treatment of disorders of consciousness.

Severe brain injuries result from traumatic brain injury ("TBI") or acquired brain injury ("ABI"). TBI occurs when a harmful event moves the brain rapidly within the skull causing damage to it (Prins et al. 2013: 1307). ABI is brain damage caused by surgery, stroke, brain tumour, infection, inflammation and ischaemia (Rowe et al. 2018: 6). Prognosis for recovery is difficult to estimate accurately for both TBI and ABI. In the United Kingdom ("UK") there is no registry to track prognosis of individuals in a PDOC (Turner-Stokes et al. 2014: 25). From the numbers of individuals in a PDOC in nursing homes in the UK, it is estimated that between 4,000-16,000 people are in a VS and nearly three times as many in a MCS (Fritz and Bunn 2015: 1). Two factors have been found to influence prognosis, the first of these being the duration of unconsciousness (Spudis 1991: 129). The longer the duration of unconsciousness the less likely recovery is (Spudis 1991: 129). The second

factor is the type of brain injury. For individuals in a VS, through non-traumatic brain injury, the probability of recovering consciousness in the first year is only 5%, whereas those who are in VS through TBI have a 35% chance of recovery within the first year (Hirschberg and Giacino 2011: 778). One-year post-TBI, 50% of persons will have "no to moderate disability" on the Disability Rating Scale (Giacino and Kalmar 1997: 36). Persons who have suffered a TBI on average recover faster and have less disability than those with an ABI (Giacino et al. 2002: 253). It is difficult to give exact numbers of people with disorders of consciousness and prognosis for recovery remains poor for those in a VS. It is therefore essential to have the most effective treatments for those most severely affected.

Accurate diagnosis of disorders of consciousness is essential to ensure that the healthcare services and families can make informed decisions about individuals' care. Unfortunately, diagnosis of those in a PDOC is highly difficult for two main reasons. Firstly, there is no gold standard for detecting awareness for those in disorders of consciousness (Giacino et al. 2014: 5). Secondly, diagnostic error is caused by variation in patients' specific characteristics which include variations in arousal level, sleep-wake cycle, pain levels, motor impairment and cognitive difficulties (Giacino et al. 2014: 5). Misdiagnosis of MCS patients as being in a VS has been reported to be as high as 41% (Schnakers et al. 2009: 1). An incorrect diagnosis can lead to the inappropriate withdrawal of life-sustaining medical care (Giacino et al. 2014: 39). It is important to have accurate methods to assess levels of consciousness.

True consciousness is not possible to observe directly. In order to reduce variability between clinicians and increase the reliability of diagnosis, 'neurobehavioral tools' are used to assess consciousness. Each of these assessment scales looks at different key behaviours of consciousness including sight, smell, hearing, pain, speech, taste, movement and communication (Seel et al. 2010: 1798). Seel et al. (2010) analysed the current literature on thirteen neurobehavioral tools using six appraisal criteria. All papers were ranked for quality, class one being 'low risk of bias' and class four being 'very high risk of bias'. The conclusions of Seel et al. (2010: 1805) are that the coma recovery scale-revised ("CRS-R") can be used to assess disorders of consciousness with only minor reservations. It has excellent content validity, meaning the extent to which it measures every single element of consciousness, and has acceptable scoring procedures and administration (Seel et al. 2010:

1800). Its content validity is enhanced by its basis on the Aspen group's definition of MCS and it has greater specificity to detect these criteria. However, the only evidence to support this comes from two highly biased studies, using un-blinded raters (Seel et al. 2010: 1803). Seel et al. (2010) recommended the following with moderate reservations, the Western Neuro Sensory Stimulation Profile ("WNSSP"), Sensory Modality Assessment Technique ("SMART"), Disorders of Consciousness Scale ("DOCS") and Wessex Head Injury Matrix ('WHIM') as each of these scales has limited evidence to support their reliability or criterion validity. This current systematised review will report on the reliability and validity of neurobehavioral tools used in the retrieved papers.

Accurate measurement of consciousness is necessary to inform individual treatment decisions. For rehabilitation centres, it is essential that the best treatment is given to individuals to ensure optimal recovery is reached. This is of particular importance if discussions around the withdrawal of treatment are to be made. Some doctors see the removal of vital nutrition and fluids as a direct contraction of their Hippocratic Oath (Sokol 2013: 1). Many in society also have concerns regarding the right to die. In 1990, the United States Supreme Court determined that quality of life is a legitimate factor when life and death are dependent on medical treatment (Fine 2005: 306). Internationally, it is now the norm to permit withdrawal of feeding tubes for those in a persistent vegetative state without application to the court (Kitzinger 2015: 2). However, in England, this still not permissible without court application, even in cases where family and clinicians agree that withdrawal of life-sustaining treatment is in the patient's best interests (Formby, Cookson and Halliday 2015: iii). The legal cost of this to the NHS is great at £122,000 per application (Formby, Cookson and Halliday 2015: iii). Treatments for consciousness or withdrawal of support is even more complex when the patient is not making the decision. With such ethical complexities, accurate diagnosis and assurance that treatment has yielded maximal recovery are essential.

Persons in a PDOC cannot consent for themselves, so ethical debate surrounds all their treatments. Standing on a tilt table can be distressing for both patients and those that care for them, due to the artificial nature of the stand (Latchem, Kitzinger and Kitzinger 2016: 26). Qualitative research conducted with family members of those in PDOC have demonstrated diverging opinions on this

treatment. Some felt that treatments like the tilt table were “unnatural” and that it was distressing to see levels of consciousness raised artificially to produce “unseeing” eyes (Latchem, Kitzinger and Kitzinger 2016: 26). Others echoed this, stating that it was “cruel” and a source of “agony” and another commented that it looked like a “medieval torture implement” (Latchem, Kitzinger and Kitzinger 2016: 26). However, many interviewees placed particular value upon physiotherapist’s ability to detect or enhance consciousness (Latchem, Kitzinger and Kitzinger 2016: 25). One interviewee stated that their relative “woke up” on the tilt table, so they wanted more of this treatment (Latchem, Kitzinger and Kitzinger 2016: 25). Several other interviewees echoed this stating that physiotherapy treatment enabled awareness to be more readily detected as their positioning aided alertness (Latchem, Kitzinger and Kitzinger 2016: 25). Whatever benefits a standing regime can produce need to be balanced with the patient’s comfort, their prior wishes and family members’ feelings.

Taking relatives and caregivers opinions into account is essential for defining appropriate research priorities. Indeed, central to the improvement of healthcare interventions is developing stronger patient and public involvement (Tritter 2009: 275). The experiences of patients that have received standing therapies could provide insights into the ability of these treatments to improve consciousness. Hence it was important to conduct patient and public involvement exercises in order to enhance this literature background and on-going research objectives. The patient and public involvement for this review took the form of semi-structured interviews at two brain injury charities (Headway and Silver Linings) and a hospital patient forum. The patient forum is a group of independent volunteers who are experts in health and hospital services. Charity group and patient forum co-ordinators were contacted by the author and they agreed to her attendance. Those present at the charity meetings were brain injury survivors, their relatives and charity co-ordinators. At each of the meetings, the author presented the preliminary results of the systematised review and proposed a qualitative discussion about the use of tilt tables. At the Headway meeting, some members had very specific memories. They commented that the movements of the tilt table were loud and abrupt and that the Velcro was very noisy. Hence the movement of the machine and the noise of the treatment could provide sensory stimulation that increases arousal in addition to the standing posture.

Medical treatments have been developed to increase people's level of consciousness. However, few have been rigorously shown to accelerate functional recovery (Whyte 2007). One pharmacological intervention has been evidenced to affect consciousness in randomised controlled trials by modulating key neurotransmitter systems. Giacino et al. (2012) found that amantadine increased rates of recovery compared to placebo over four weeks for persons in VS and MCS. After four weeks of treatment, 31% of the placebo group remained in VS compared to only 18% of the amantadine group (Giacino et al. 2012: 823). Central thalamic deep brain stimulation ("CT-DBS") is another treatment designed to modulate levels of consciousness (Giacino et al. 2014: 10). This device is surgically implanted with the objective of activating cortical networks that have been downregulated through brain injury (Giacino et al. 2014: 10). However, most data from earlier studies of CT-DBS on those in a PDOC do not demonstrate significantly different rates of recovery to that without this surgical intervention (Shah and Schiff 2010). Medical treatment for consciousness is an area that requires on-going research to assess its efficacy.

Multiple authors have demonstrated standing treatments' ability to affect consciousness, but no systematised review has collated this evidence (Luther et al. 2007; Krewer et al. 2015; Elliott et al. 2005). There is a discrepancy in their use between rehabilitation centres as optimal dosage and initiation of treatment times are unknown. Despite this, assisted standing, using a tilt table with or without integrated stepping, is a regular treatment method. Two surveys in Australia and the UK found tilt table training for consciousness to be the in the top five most commonly cited uses for standing regimes (Chang et al. 2004: 52; Moore and Jones 2011: 4). In the UK, 66% of physiotherapists had access to a tilt table, and of these 48% indicated they used the tilt table two to three times per week per patient (Moore and Jones 2011: 4). This is consistent with Chang et al. (2004: 52) who found that 67.4% of respondents completed early mobilisation using the tilt table and twelve respondents reported using the tilt table more than once a week (Chang et al. 2004: 52). Tilt table usage is usual practice and therapists have good access in the UK and Australia. The treatment goal to increase levels of arousal is common-place but the evidence underpinning this practice is limited. The objective of this review is to review the evidence base to assess this efficacy.

In order to best treat disorders of consciousness, it is important to understand the neurobiology that causes unconsciousness. The primary pathophysiology is the disruption of neurons and network mechanisms within the thalamus, cerebral cortex and striatum (Giacino et al. 2014: 4). This is known as the mesocircuit model (Schiff 2010), which hypothesises that widespread disconnection or neuronal cell death causes downregulation of anterior forebrain function (Giacino et al. 2014: 4). This theory postulates that a reduction of corticostriatal, thalamocortical and thalamostriatal outflow reduces afferent input to the medium spiny neurones of the striatum, which prevents these neurones from reaching firing threshold (Grillner et al. 2005: 367-368). Neurons within the central thalamus are known be progressively disrupted proportionally to the severity of brain injury (Maxwell et al. 2006: 478). It is the inability of these disrupted neurons to reach firing threshold is thought to produce unconsciousness.

The second hallmark of disorders of consciousness is the reduction in cerebral blood flow and cerebral metabolism. Fluorodeoxyglucose positron emission tomography (FDG-PET) measures brain metabolism and studies using this have shown a decrease in metabolic function for those in a VS (Levy et al. 1987: 673). Research has identified key areas of reduced metabolism, including the frontoparietal network and lateral associate cortices (Lull et al. 2010: 1101-1104). Impairment of cerebral blood flow has been demonstrated in MCS patients who showed decreased cerebral blood flow in comparison to controls within the medial prefrontal and midfrontal cortical regions (Liu et al. 2011: 1518). Reduction in cerebral metabolism and cerebral blood flow is therefore associated with disorders of consciousness.

The exact mechanisms surrounding recovery of consciousness are not well understood. In addition to this, it is not known how standing mediates increases in consciousness, so it is important to consider here the neurobiological mechanisms that could control this. For example, the physiological stimulus that occurs when placing a person in a standing position could trigger increases in alertness. Riberholt et al. (2013) have demonstrated that tilt table standing increases the heart rate of healthy controls and those in disorders of consciousness. When performing an active stand there are physiological mechanisms to maintain homeostasis, most crucially sufficient blood flow to the brain. On standing gravity causes blood to pool in the lower extremities, this lowers arterial blood pressure

triggering baroreceptors located in the carotid and aortic walls (Olufsen et al. 2005: 2). Parasympathetic withdrawal elevates heart rate and sympathetic activation raises vascular tone and cardiac contractility causes further increases in heart rate (Danielson and Otteson 2001: 75-77). Concurrently cerebral autoregulation leads to vasodilatation of cerebral arterioles. These homeostatic mechanisms maintain blood pressure with changes in position. In order to maintain blood pressure, these mechanisms will still occur during a passive stand for a person in a PDOC. These physiological responses, including increased heart rate could affect alertness.

On the other hand, loss or impairment of cerebral pressure autoregulation is common in those with severe brain injury, which could help to explain variance in the efficacy of tilt table treatments. Cerebral autoregulation is the intrinsic ability to maintain cerebral blood flow over a range of blood pressures (Rangel-Castilla et al. 2008: 1-2). This is a complex process involving myogenic, neurogenic and metabolic mechanisms (Rangel-Castilla et al. 2008: 1-2). Severe brain injury can disrupt all of these mechanisms. Impaired cerebral autoregulation can cause orthostatic intolerance, vasovagal or syncope, during head-up tilt (Riberholt et al. 2016: 1). When a person is mobilised, orthostatic intolerance manifests itself as a rapid decrease in mean arterial pressure or tachycardia (Riberholt et al. 2013: 1). This has been confirmed through tilt table testing comparing those in disorders of consciousness with healthy controls (Riberholt et al. 2013). Mean arterial pressure increased for controls but decreased for the patient group (Riberholt et al. 2013: 1). Recurrent syncope is a commonly cited reason for stopping standing treatments and often limits rehabilitation. It is therefore important to understand how to safely rehabilitate individuals using standing protocols.

An intact vestibular system will signal changes in motion to a person even if they are in a disorder of consciousness, so a change of position could stimulate increased alertness. Vestibular dysfunction is common in traumatic brain injury. Dizziness and disequilibrium are reported in 40-60% of persons (Gannon et al. 1978: 404). However, many with an ABI will have an intact vestibular system. There are several components of the vestibular system which will signal a change in position when a person is positioned from lying to standing using an assisted standing device. The vestibular portion of the eighth cranial nerve informs the brain of angular and linear movements of the head (Highstein and

Holstein 2006:157). This means that when a person in a PDOC is stood vestibular system emits electrical discharges to the CNS, which could indirectly promote alertness.

Positioning a person in a standing position can induce some noxious stimuli through stretching to tight or spastic muscles. As persons in disorders of consciousness have shown a cortical response to painful stimuli, it could be the stimulation of pain receptors that increases alertness. Being positioned in standing on a tilt table can be uncomfortable despite clinicians' efforts to avoid any discomfort. Tommaso et al. (2013) found reliable cortical responses to painful laser stimulation for persons in both VS and MCS. This is replicated by other authors who found similar cortical activation between those in a MCS and controls when stimulated by an electrical stimulus which was deemed painful by the healthy control group (Boly et al. 2008). A response to noxious stimuli and muscular stretch could be a cause of increased arousal when persons in a PDOC are placed in a standing position.

Despite standing regimes' widespread use, there is no systematised review on how they affect consciousness. Several neurobiological mechanisms support standing treatments' ability to change consciousness. However, in order to allow effective prescription collated evidence is required. Clinicians need to know if their treatment is effective in order to balance it against side effects. Healthcare providers need to know if this treatment is efficient in order to balance it against finite resources. It is the intention of this systematised review to assess the effects of standing on consciousness for those in a PDOC.

Chapter 3: Methods

Review epistemology and methodology

It is important to discuss the research philosophy that underpins this systematised review prior to outlining the methods. A research question and hypothesis were generated to evaluate the current literature on standing. This review is searching for an underlying truth to give an unbiased answer. This is consistent with a positivist ontology, which is defined as a reality existing externally to the researcher and investigation should occur through thorough scientific methods (Gray 2014: 21-25). However, a strict positivist ontology does not fully explain the wide-ranging variables in human

physiology or the fallibility of observers that occurs in health research. Therefore, a post-positivist paradigm supports this systematised review.

Post-positivism maintains that there is an independent reality, but observers are inherently fallible, hence the truth is approximated not explained (Gray 2014: 23). The hypothesis was tested against the current literature in order to look for the truth. Hence, the epistemological perspective is Popper's hypothetico-deductive theory (Popper 2002). This theory involves devising a hypothesis and comparing it against the available data (Ippoliti, Sterpetti and Nickles 2016: 100-102). In this case, the hypothesis was tested against the evidence provided in the papers yielded by the search strategy. The main limitation of this theory is that it assumes cause and effect (Ippoliti, Sterpetti and Nickles 2016: 100-102). Hence, the hypothesis assumes being positioned in standing causes a change in level of consciousness. To ensure this connection is not assumed, this review investigated, other causes of changes in consciousness from the primary papers.

A quantitative perspective supports the methodology for this review as all studies included will have their numerical data analysed. This data comes from the measurements of consciousness after a standing treatment as measured through neurobehavioral assessment. The method followed a PRISMA-P format which ensured objective, systematic and comprehensive reporting (Shamseer et al. 2015).

Review questions

1. Does consciousness level change when persons in a PDOC are elevated into a standing position?
2. Does a standing regime increase consciousness in comparison to standard therapy for persons in a PDOC?

Objective: To identify all the studies testing the effect of single standing treatment or assisted standing regimes on consciousness for individuals in a PDOC. To assess them for quality and synthesise the results.

To test the following hypotheses:

Null hypothesis:

1. There is no difference in median neurobehavioral scores for the intervention compared to control groups after a single standing treatment session.

2. There is no difference in the number of persons in consciousness states (VS, MCS and emergent MCS) for the intervention compared to control groups after a single standing treatment session.

3. There is no change in median neurobehavioral score for the intervention compared to control groups after a standing regime.

4. There is no difference in the number of persons in consciousness states (VS, MCS and emergent MCS) for the intervention compared to control groups after a standing regime.

Alternate hypothesis

1. There is a statistically significant difference in median neurobehavioral scores for the intervention compared to control groups after a single standing session.
2. There is a statistically significant difference in the number of persons in consciousness states (VS, MCS and emergent MCS) for the intervention compared to control groups after a single standing treatment session.
3. There is a statistically significant difference in median score for the intervention compared to control groups after a standing regime.
4. There is a statistically significant difference in the number of persons in consciousness states (VS, MCS and emergent MCS) for the intervention compared to control groups after standing regimes.

Review design

Two researchers, Harriet Ng ("HN") and Dr Andrew King ("AK"), completed this systematised review which followed a PRISMA-P protocol (appendix 1.1). This protocol was chosen as it is specifically designed for transparency and clarity of reporting (Liberati et al. 2009: 4-5). This ensured sufficient quality assessment of the included papers (Moher et al. 2007: 451-453). The avoidance of poor reporting was essential to establish the value of the systematised review to clinicians, policymakers and other users (Liberati et al. 2009: 1).

Table 3.0 Literature search

Stage	Search objective	Search action
1.	Ethical approval sought from Coventry University. Submitted research proposal to Prospero database of systematic reviews.	Ethical approval granted by Coventry University on 08/02/2018 (P62995). Registration as a review by Prospero on 12/02/2018 (CRD42018084069).
2.	Two researchers ("HN" and "AK") completed the search. Using a combination of search terms outlined in appendix 1.2-4. This search was completed in the following databases:- • MEDLINE • CINAHL • AMED • PEDro No language restrictions or study quality restrictions were made (see "*Types of studies" page 20 for full details)* Key words were searched in the Cochrane Database.	Completed on 24/2/18-25/3/18.
3.	One researcher ("HN") searched for grey literature in:- • British library integrated catalogue • EThOS (e-theses online service) • Zetoc (The British Library's Electronic Table of Contents) • Proquest (Dissertations & Theses) • Association of Charted Physiotherapists in Neurology magazine - Synapse • The Chartered Society of Physiotherapy – Frontline	Completed on 6/8/18-7/8/18.
4.	One researcher ("HN") used keywords to search two trial registers WHO International Clinical Trials Registry Platform (2017) and U.S. National Library of Medicine (2013) for unpublished studies.	Completed 27/2/18.
5.	Two researchers ("HN" and "AK") independently reviewed the titles and abstracts of retrieved articles and removed those that were irrelevant. Papers that did not provide enough information in the abstract were highlighted to be read as full text articles.	Completed on 24/2/18-25/3/18.
6.	Post citation searching of relevant full text articles was completed by ("HN"), using the main authors name to review all their publications in *Scopus*. Then using the title of the included texts to review all publications that had referenced them.	Completed 25/3/18-4/4/18.
7.	The review author pair ("HN" and "AK") decided on the studies for inclusion. Disagreement was	The appropriate articles for inclusion from all searches were agreed between the review author pair.

	resolved through discussion and adherence to the inclusion criteria. The reasons for exclusion were documented (see appendix 1.5).	
8.	To merge full search results and remove duplicates reference management software was used *Proquest Refworks (2017*).	Full text articles saved and duplicates removed.
9.	Relevant full texts were retrieved and purchased where needed.	All relevant full texts were accessed.
10.	One reviewer read ("HN") the full texts to ensure compliance with inclusion criteria in discussion with the second researcher ("AK") (see table 3.1).	Completed between 4/4/18-20/4/18.
11.	Correspondence was planned with authors for clarification on published studies by one reviewer ("HN").	No clarification was required.
12.	One reviewer ("HN") completed data collection using an amended Cochrane data collection (2014) form and additionally the Downs and Black (1998) data collection form for observational studies (see appendix 1.6 and 1.7). Assessment of bias was completed using these data collection forms.	Completed between 20/4/18-1/5/18.

Table 3.1 Inclusion criteria for the primary articles as defined by 'P.I.C.O'

A 'P.I.C.O' method has been used to form constructive inclusion criteria (Huang et al. 2006: 359-263).

Person	**Adults (>18 years old) of either gender. With a diagnosis of coma, VS or MCS.** This diagnosis needs to be consistent with the definitions of coma, VS and MCS by Giacino et al. (1997) or the "Prolonged disorders of consciousness National clinical guidelines - Report of a working party 2013" **(**Turner-Stokes 2014**)**. These definitions best differentiate between the states of consciousness.
Intervention	The intervention can be given as a single treatment session or as a standing regime. A standing regime is defined here as a treatment period of over two weeks as it has been reported that two weeks of sensory stimulation is necessary for there to be a significant effect on consciousness (Oh and Seo 2003). • Tilt table • Tilt table with integrated stepping also known as ("ERIGO") • Other fully supportive passive standing machinery (with or without integrated stepping)
Comparator	This will be dependent on the procedure of study. The primary comparison will between standard treatment alone and standard treatment with additional standing practise. The scores pre-and post-treatment can be compared from the neurobehavioral assessment tools. Standard treatment was defined as any of the following; • Physiotherapy/Physical therapy • Regular nursing interventions • Occupational Therapy • Speech and language therapy including swallowing treatment • Medical care including neuro-pharmacological interventions
Outcome	**Primary outcome** Neurobehavioral score as assessed through any of the following tools; • GCS, CRS-R, SMART, WHIM, Sensory Tool to Assess Responsiveness ("STAR"), Levels of cognitive function ("LCF"), or other neurobehavioral assessment tool as outlined by the study **Secondary outcome** Physiological assessment including; heart rate, blood pressure, respiratory rate or increased eye opening.

Exclusion criteria

Any abstracts that did not include the keywords listed in the 'P.I.C.O' table were excluded, as they would not answer the research question. Articles that did not assess standing's effect on consciousness were excluded, for example, on populations not in disorders of consciousness. Any study conducted on children was not appropriate due to their immature brain recovering differently (Anderson, Spencer-Smith and Wood 2011). Indeed, including a paediatric population would have produced an unnecessarily heterogeneous study population and could obscure treatment effect. Heterogeneity was also controlled by excluding studies on persons who sustained a congenital brain injury due to its differing aetiology. Studies on active standing were excluded as this is not possible for the study population. In addition, to this animal studies were excluded as they would not be able to answer the research question.

(i) the data bases/search engines to be used

Search

To minimise bias two researchers ("HN" and "AK") exhaustively searched the databases outlined below. This included subject-specific databases to increase the likelihood of retrieving pertinent studies. To find as many relevant studies as possible, one researcher ("HN") searched the key author's written articles and their reference lists to look for all related papers. In addition to this, articles that had referenced the key authors were exhaustively searched. To find unpublished studies a search of trial registers (WHO International Clinical Trials Registry Platform (2017) and U.S. National Library of Medicine (2013)) was completed. Keywords were used to search for grey literature including conference proceedings, presentations and theses in the British library integrated catalogue. The EtHOS database and Proquest (Dissertations and Theses) were used to further search for PhD theses. Zetoc was used to look for relevant conference proceedings and journal articles. Finally, specialist professional magazines were searched for relevant articles of grey literature.

Electronic Databases
MEDLINE
CINAHL
AMED
PEDro
The Cochrane library
SCOPUS

Grey literature sources
British Library Integrated Catalogue
EThOS (e-theses online service)
Zetoc (The British Library's Electronic Table of Contents)
Proquest Dissertations and Theses
Association of Charted Physiotherapists in Neurology magazine - Synapse
The Chartered Society of Physiotherapy – Frontline

(ii) Types of studies

No limit was set on date or language so that the whole evidence base could be analysed. Grey literature was included in this study in order to search for specialist opinions not available in mainstream databases. Some information is only available through grey literature sources, such as preliminary results of research, so these sources were analysed for further insights into this subject area. There was no quality restriction on study design as the emerging nature of this field required the inclusion of case and cross-sectional studies. Other authors have supported the inclusion of lower quality studies that are able to answer the research question. Aveyard and Sharp (2010: 78-80) argue that emerging areas of research will have smaller amounts of high-quality research information

available and therefore discussion pieces and expert opinion adds necessary insight. Important information would be missed if lower quality articles were not included in this systematised review. Ciliska, Thomas and Fitzpatrick-Lewis (2009: 6) concur with this stating that studies without control groups can be usefully included in systematic reviews especially when there are no other studies to include. Indeed, their analysis of systematic reviews that had included such studies found no association between effect size and study quality (Ciliska, Thomas and Fitzpatrick-Lewis 2009: 19). Nevertheless, to allow readers complete transparency on study quality a clear grading of bias will be displayed in the results, thus, showing the reliability and validity of each of the included literature.

(iii) Key words

In order to yield papers pertinent to the research questions, it was divided into three key themes, population, intervention and outcome. This allowed for the appropriate combination of the themes in order to find relevant articles. To broaden the search for all relevant synonyms the keywords for each theme were searched in CINAHL (Headings) and Medline (MeSH). To exhaustively search all major databases truncations and wildcards were used to combine the root word being with multiple endings or variations of the word (Higgins and Green 2011).

Variations for search engines	**Example word**	**Examples variations of the word**
Wild card ('?')	Injur(?)y	Injuries, Injured
Truncation ('*')	Stand*	Stands, standing

(iv) Population

The keywords and synonyms were chosen by directly reflecting the aetiologies that cause a PDOC. This includes trauma, vascular events, hypoxia, hypo-perfusion, infection, inflammation and toxic or metabolic disorders.

(v) Types of interventions

There are two fully assisted standing devices the 'tilt table' and 'ERIGO'. To maximise the search synonyms for "standing frame" and "stand" were completed. To enhance this search further truncations of "stand(*)" were used by adding appropriate symbols for each database (Cronin, Ryan

and Coughlan 2008: 38). Terms linked to rehabilitation and all types of therapists were used to include all possible treatment providers.

(vi) Types of outcomes

The main outcome is a change in consciousness and therefore keywords pertaining to this were used. Synonyms of these keywords were searched for in all major databases. Neurobehavioral tools assess levels of consciousness; hence they were included in the outcome search terms to yield related-papers.

Planned search

A comprehensive search of all databases was completed using the search terms and Boolean Logical operators outlined below. Synonyms were joined using 'OR' and the terms for population, intervention and outcome with be joined with 'AND'. For a proposed search strategy see table 3.2 and for the full search terms and search strategy see table 3.2 and appendix (1.2-4).

Table 3.2 Search strategy CINAHL (see appendix 1.2 for full search strategy)

PICO	Combination of terms as appropriate
Population A **Aetiology Vascular event**	(S1 OR S2 OR S3 OR S4 OR S5 OR S6)
Population B **Traumatic Brain Injury**	S7
Population C **Hypoxia**	S8
Population D **Infection**	(S9 OR S10)
Population E **Toxic/Metabolic**	(S11 or S12)
Population F **Prolonged disorder of consciousness terminology**	(S13 OR S14 OR S15 OR S16 OR S17 OR S18)
Intervention 1 **Standing devices**	(S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31)
Intervention 2 **Stand**	(S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S 38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44)
Intervention 3 **Rehabilitation**	(S45 OR S46)
Outcome - change of consciousness	(S47 OR S48)
Population	Combination of all the terms for population e.g. (S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18)
Intervention 1 **Standing devices**	Combination of all intervention 1 terms e.g. (S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31)
Intervention 2 **Stand**	Combination of all intervention 2 terms e.g. (S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S 38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44)
Intervention 3 **Rehabilitation**	Combination of all intervention 3 terms e.g. (S45 OR S46)
Outcome	Combination of all outcomes e.g. (S47 OR S48)
P I1 O	Population AND Intervention 1 AND Outcome
P I2 O	Population AND Intervention 2 AND Outcome
P I3 O	Population AND Intervention 3 AND Outcome

Data collection process

A consensus was reached through discussion between reviewers ("HN" and "AK") on the final articles for inclusion. All data collection was performed by HN. This was completed using the customised "Data collection form for intervention review – Randomised controlled trials and non-randomised controlled trials" (Green and Higgins 2008). Additional data collection was performed on observational trials using Downs and Black (1998) to give greater clarity on their reporting, as this data collection method has been shown to be sensitive for non-randomised studies (Downs and Black 1998: 379). A three-stage evaluation of the Cochrane data collection tool was completed during its creation by prominent statisticians, review authors and epidemiologists (Higgins et al. 2011: 2). The use of this form ensures the risk of bias is properly assessed and a clear summary of study reports is provided. The customisation was completed by one researcher ("HN") through trialling this form on included studies. This customisation allowed comprehensive and efficient collection of data by removing irrelevant sections from the original form. Some inconsistency between reviewers has been reported using this tool for the assessment of bias (Armijo-Olivo et al. 2014). This was avoided between both reviewers ("HN" and "AK") through adherence to the Cochrane Handbook (Higgins and Green 2011).

Data items

The main data items were decided prior to data extraction as outlined below, this avoids introducing bias that might mislead the reader (Moher et al. 2014: 12). These data items allow for appropriate statistical and narrative analysis.

Table 3.3 Planned data collection

Eligibility	The aims of the study and methods were cross-referencing against the 'P.I.C.O' criteria to ensure the paper was appropriate for inclusion.
Characteristics of the study	Notes were made on the aims of the study, unit of allocation, methods and results. The methods and unit of allocation were required for statistical analysis and assessment of methodological heterogeneity.
Characteristics of Participants	The population's essential traits were collected from each paper. This allowed for comparison between studies to assess for clinical heterogeneity.
Intervention groups	The essential characteristics of the intervention were recorded to assess its validity and allow comparison between primary papers. This included the timing and duration of treatment, the treatment provider and the numbers of participants randomised. This information was necessary to compare methodological heterogeneity.
Outcomes	The primary outcome was level of consciousness. Which is scored using a neurobehavioral tool or another reliable method for assessing consciousness. For a single session, this should be recorded pre and post-intervention. For a standing regime, this was pre and post the defined regime period. This outcome is the most objective measure of change in consciousness. The secondary outcome was physiological changes. For instance, heart rate, blood pressure, respiratory rate and increased eye-opening. Riberholt et al. (2013) used increased time with eyes open as a physiological indication of consciousness. Any other outcomes included in primary studies were not be recorded as they were not relevant to the research objectives of this systematised review.
Main study findings and conflicts of interest	The main results of the study were documented. Any conflicts of interests were noted for potential biases.
Risk of bias assessment	The amended Cochrane data collection form (2014) and Downs and Black checklist (1998) assessed the risk of bias. This categories risk of bias as high, medium or low. This information was used to assist statistical analysis.
Data analysis	The main items for statistical analysis were treatment effect, numbers of missing participants, the unit of analysis, unit of measurement, statistical methods used and the main results. The use of a power calculation was essential to ensure an adequate sample size and therefore required extraction from each primary paper. The unit of measurement was recorded for validity analysis.
Key conclusions of study authors	The author's main conclusions were documented to give an appropriate narrative summary.
References to other relevant studies	Relevant studies were noted to show the links in the literature.

Validity and Reliability of studies

The articles retrieved were analysed for validity and reliability using the amended Cochrane Collaboration tool. The embedded risk of bias tool analyses many forms of bias including design, sampling and procedural. It was important to assess for design bias as this indicates the validity of the study demonstrating how credible the results are. Sampling and procedural biases will reduce the reliability and consequently the replicability of results. The tool was chosen to facilitate transparent assessment of bias (Jørgensen et al. 2016: 4). However, it has been criticised for lacking assessment of conflicts of interest and funding biases (Jørgensen et al. 2016: 12). This has been added as an extra domain to improve assessment of bias. In order to improve the clarity of reporting further an additional analysis was performed on observational studies. This is because cohort and case-control studies have essential design differences and it is important to review them differently (Downs and Black 1998: 377). The Cochrane data collection form has the same assessment questions for randomised controlled trials but lacks the specificity of Downs and Black for non-randomised studies. Therefore, the quality assessment of observational studies was improved using Downs and Black checklist (Downs and Black 1998). Verbatim quotes were used to answer the domains. The 'risk of bias tables' (4.2-4.4) display the Downs and Black risk of bias scores and Cochrane risk of bias rankings.

Data Analysis

Effect size calculation

The first stage of data analysis was to find or calculate treatment effect sizes. To assess the effect size of standing treatments' on consciousness Cohen's d statistic was used (Cohen 1971). Where there was no control group the pre and post-treatment scores were used to calculate the mean difference.

$$\textbf{Effect size} = \frac{[\text{Mean of the experimental group}] - [\text{Mean of the control group}]}{\text{Pooled standard deviation}}$$

$$\textbf{Effect size} = \frac{[\text{Mean post-treatment}] - [\text{Mean pre-treatment}]}{\text{Pooled standard deviation}}$$

If all the original data sets were not available, the percentage change pre and post-treatment was calculated. If insufficient information was available from the primary papers no meaningful statistical analysis was completed. In this case, the results of these papers were explored narratively.

Statistical heterogeneity

There was an intention to analyse statistical heterogeneity as advised by the Cochrane Handbook. This recommends using the Chi-squared statistic with the quantifying I^2 statistic to assess statistical heterogeneity. The Chi-squared test alone has low statistical power with small sample size studies, hence the I^2 statistic is additionally recommended (Green and Higgins 2008). This would only be justified if there was sufficient homogeneity in the study design, populations and outcomes between studies (Charrois 2015: 146). It was recognised that studies in this area are very diverse and narrative analysis might have to be used.

Chapter 4: Results of the literature search

The PRISMA flowchart (figure 1) shows 707 retrieved titles through database searching. Post-citation searching of the three articles identified through full text review retrieved a further seven articles (Elsevier 2018). After a final review of full text articles, ten were deemed appropriate for inclusion through reviewer discussion. No systematic reviews or grey literature met the inclusion criteria. Papers that readers would expect to be included in this systematised review, but on further inspection did not meet the inclusion criteria, are listed below in appendix 1.5 (Higgins and Green 2011). The characteristics of the primary research articles included in the review are shown in table 4.0-4.1.

All ten articles that were retrieved included participants in disorders of consciousness who underwent standing treatment. Five articles study the effects of single stand assessments and five articles assessed the effect of standing regimes on consciousness. The setting used can be divided into acute and sub-acute settings. Three studies were conducted in an acute intensive care unit; one in Brazil (Toccolini et al. 2015) and two in Italy (Bartolo et al. 2016; Frazzitta et al. 2016). The remainder of the studies were in sub-acute settings; three in rehabilitation units (Taveggia et al. 2015; Krewer et al. 2015; Luther et al. 2007) and two brain injury units (Riberholt et al. 2013; Greco et al. 2013). These were conducted in Germany, Denmark and Italy. The other two studies did not state the

setting in which the research was conducted (Elliott et al. 2005; Wilson et al. 2013). For each setting the standing device used was either the tilt table, the ERIGO or both.

The methodological quality of the selected studies, including the risk of bias has been analysed narratively and statistically. The results of the included studies have been analysed for statistical, study and clinical heterogeneity. Finally, the authors results have been displayed graphically and where possible the treatment effect has been described.

Figure 1: PRISMA flow chart

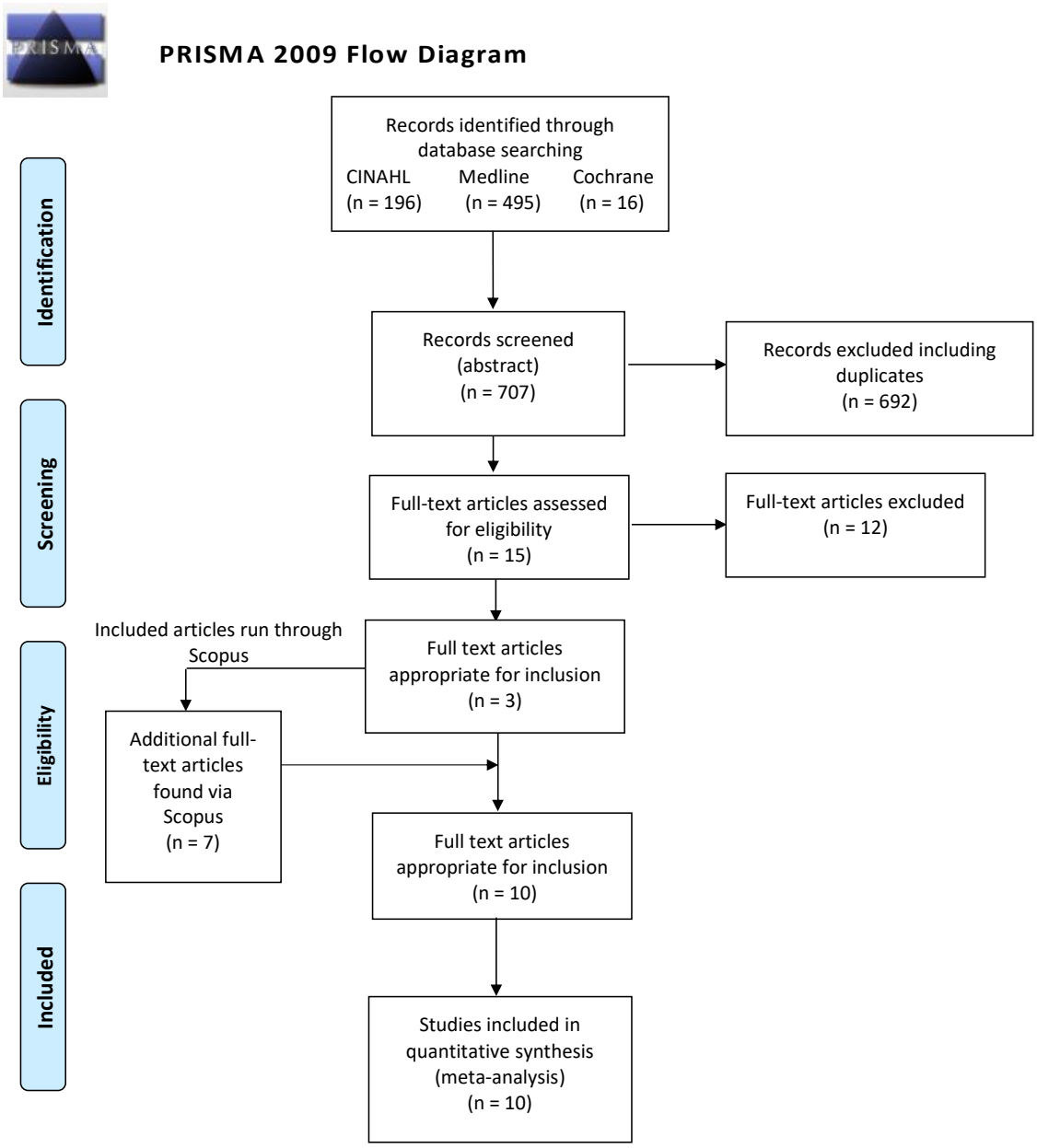

Table 4.0 Population characteristics of included studies – single stand studies

Study	Study type	Study location	Setting	Outcome measures for consciousness	Population characteristics	Intervention
Elliott et al. (2005) (L. Elliott, M. Coleman, A. Shiel, B. A. Wilson, D. Badwan, D. Menon, and J. Pickard)	Case series	United Kingdom	Not stated	WHIM	**N = 12** Ages 19–71 yrs 8 M, 4 F VS (N=5) MCS (N= 7)	**Participants had single treatments** • On a tilt table at 85° **Assessment performed** 1. Supine 2. Standing (tilt table)
Greco et al. (2013) (A. Greco, M.C. Carboncini, A. Virgillito, A. Lanatà, G. Valenza and E.P. Scilingo)	Case series	Italy	Brain Injury Unit	EEG Power spectral analysis Symmetry index	**N = 3** Ages 56-73 yrs 1 M, 2 F MCS (N = 3)	**Participants had a single session** • At a maximum of 60 degrees using the ERIGO tilt table. Time of assessment not stated.
Luther et al. (2008) (M. S Luther, C. Krewer, F. Müller and E. Koenig)	Randomised crossover pilot trial	Germany	Neuro-rehabilitation hospital	CRS-R	**N = 9** Ages 20-51 yrs 5 M, 4 F VS (N= 3) MCS (N = 6)	Participants had two single treatment sessions 1. On a conventional table 2. On an ERIGO a tilt table with integrated stepping Time of assessment not stated.
Riberholt et al. (2013) (C. G. Riberholt, J. B. Thorlund, J. Mehlsen and A. M. Nordenbo)	Case series	Denmark	Traumatic Brain Injury Unit	Time period with eyes open	**N = 16** Ages 18-74 yrs 10 M, 6 F VS (N =3) MCS (N = 11) Aware (N = 2)	**Participants had a single session** • Tilted head-up to 30°, after 1 minutes further tilted to 60° • Final tilt to 80° **Assessment performed** • 30 minutes prior to treatment • During standing treatment
Wilson et al. (2013) (B. A. Wilson, S. Dhamapurkar, C. Tunnard, P. Watson, and G. Florschutz)	Case series	United Kingdom	Not stated	WHIM	**N = 16** Ages 27-70 yrs 10 M, 6 F VS (N = 8) MCS (N = 8)	**Participants had a single session** • Sitting • Standing with assistance of tilt table 90˚ unless the participant was unable to tolerate this, then elevation to 60˚, 70˚ or 80˚. **Assessment performed** In Supine, sitting (without head support) and standing.

Table 4.1 Population characteristics of included studies – standing regime

Study	Study type	Study location	Setting	Outcome measures for consciousness	Population characteristics	Intervention
Bartolo et al. (2016) (M. Bartolo, S. Bargellesi, C. A. Castioni, D. Intiso, A. Fontana, M. Copetti, F. Scarponi, D. Bonaiuti)	Prospective observational study	Italy (14 units)	Neurological Intensive Care Units	GCS DRS LCF ERBI GOS	**N = 102** Ages 45.6–69.7 yrs 60 M, 42 F GCS at baseline 6.5 (5.7–7.3)	**Participants were randomised to either** 1. An early mobilisation regime – sitting and standing using a tilt bed/table to ≥40°. 2. A non-mobilisation group **Assessment performed** • Baseline, 1st evaluation, 2nd evaluation, 3rd evaluation, 4th evaluation and ITU discharge
Frazzitta et al. (2016) (G. Frazzitta, I. Zivi, R. Valsecchi' S. Bonin, S. Maffia, K. Molatore, L. Sebastianelli, A. Zarucchi, D. Matteri, G. Ercoli, R. Maestri and L. Saltuari)	Single-blind randomised clinical trial	Italy	Intensive Care Unit	CRS-R DRS LCF	**N = 31** Ages 22-82 yrs 20 M, 12 W VS (N = 31)	**Participants were randomised to either** 1. An early stepping verticalisation protocol (30 minutes) plus traditional therapy (30 minutes) 2. Conventional in-bed physiotherapy (60 minutes a day) Five times a week for three consecutive weeks. **Assessment performed** At admission**,** intensive Care Unit discharge and neurorehabilitation discharge
Krewer et al. (2015) (C. Krewer, M. Luther, E. Koenig, F. Müller)	Single blind Randomised Controlled Trial	Germany	Rehabilitation unit	CRS-R	**N = 44** Ages 23–74 yrs 26 M, 18 F VS (N = 14) MCS (N= 30)	**Participants were randomised to either** 1. Tilt table standing 2. ERIGO standing Ten 1-hour sessions over a 3-week period. **Assessment performed** • Before and after the intervention period (3-week and 6-week follow-up)
Taveggia et al. (2015) (G. Taveggia, I. Ragusa, V. Trani, D. Cuva, C. Angeretti, M. Fontanella, P. Paolo Panciani and A. Borboni)	Randomised controlled trial	Italy	Neurorehabilitation hospital	CRS-R LCF	**N = 12** Ages 47- 79 yrs 4 M, 4 F VS (N = 7) MCS (N= 5)	**Participants were randomised to either** 1. Study group A verticalisation with a tilt table at 65° with robotic lower limb movement. 2. Control group B standing with no lower limb movement. 3. Then each group repeated the other treatment method. 30 minutes three times a week for 24 sessions. **Assessment performed** • Before and after treatment

Study	Study type	Study location	Setting	Outcome measures for consciousness	Population characteristics	Intervention
Toccolini et al. (2015) (B. F. Toccolini, E. Fernanda Osaku, C. Rejane Lima de Macedo Costa, S. Nogueira Teixeira, N. Lamberti Costa, M. Fernanda Cândia, M. Aparecida Leite, C. Eduardo de Albuquerque, A. Cezar Jorge and P. A. Delfino Duarte)	Prospective cohort study	Brazil	Intensive care unit	GCS	**N = 23** Ages 42.5-79.5 yrs 15 M, 8 F GCS not recorded prior to treatment.	**Eligible patients were included** 1. Stood on a tilt table (30°, 45°, 60°, 75°, and 90°) Daily standing for 30 minutes until discharge from ITU. **Assessment performed** • Day 1, day 2 and day of discharge • Recordings at each inclination (30°, 45°, 60°, 75°, and 90°)

Study Quality

The assessment of the risk of bias has been analysed through the Cochrane risk of bias tool (2014) for all studies in table 4.2 and 4.3. The Downs and Black checklist was an additional analysis for the non-randomised studies included in table 4.4.

Table 4.2 Risk of bias assessment using Cochrane risk of bias tool – single stands

Study	Adequate sequence generation?	Allocation concealment?	Blinding? (Participants and personnel)	Blinding? (All outcomes-clinical assessor)	Incomplete outcome data addressed	Free of selective reporting	Free of other biases
Elliott et al. (2005) (L. Elliott, M. Coleman, A. Shiel, B. Wilson, D Badwan, D. Menon, and J. Pickard)	N/A	N/A					
Greco et al. (2013) (A. Greco, M.C. Carboncini, A. Virgillito, A. Lanatà, G. Valenza and E.P. Scilingo)	N/A	N/A					
Luther et al. (2008) (M. S Luther, C. Krewer, F. Müller and E. Koenig)							
Riberholt et al. (2013) (C. G. Riberholt, J. B. Thorlund, J. Mehlsen and A. M. Nordenbo)	N/A	N/A					
Wilson et al. (2013) (B. A. Wilson, S. Dhamapurkar, C. Tunnard, P. Watson, and G. Florschutz)	**N/A**	**N/A**					

Key

Level of bias	**Low**	**Unclear**	**High**
Corresponding colour			

Table 4.3 Risk of bias assessment using Cochrane risk of bias tool – single stands

Study	Adequate sequence generation?	Allocation concealment?	Blinding? (Participants and personnel)	Blinding? (All outcomes-clinical assessor)	Incomplete outcome data addressed	Free of selective reporting	Free of other biases
Bartolo et al. (2016) (M. Bartolo, S. Bargellesi, C. A. Castioni, D. Intiso, A. Fontana, M. Copetti, F. Scarponi, D. Bonaiuti)	N/A	N/A					
Frazzitta et al. (2016) (G. Frazzitta, I. Zivi, R. Valsecchi, S. Bonin, S. Maffia, K. Molatore, L. Sebastianelli, A. Zarucchi, D. Matteri, G. Ercoli, R. Maestri and L. Saltuari)							
Krewer et al. (2015) (C. Krewer, M. Luther, E. Koenig, F. Müller)							
Taveggia et al. (2015) (G. Taveggia, I. Ragusa, V. Trani, D. Cuva, C. Angeretti, M. Fontanella, P. Paolo Panciani and A. Borboni)							
Toccolini et al. (2015) (B. F. Toccolini, E. Fernanda Osaku, C. Rejane Lima de Macedo Costa, S. Nogueira Teixeira, N. Lamberti Costa, M. Fernanda Cândia, M. Aparecida Leite, C. Eduardo de Albuquerque, A. Cezar Jorge and P. A. Delfino Duarte)	N/A	N/A					

Key

Level of bias	Low	Unclear	High
Corresponding colour			

Table 4.4 Assessment of quality of observational studies, using checklist of Downs and Black (1998)

		Checklist																										
		Reporting										External Validity			Internal Validity-Bias							Internal Validity-Confounders						Power	
Study Number	First Author	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	
		Study aim	Main outcome	Subject characteristics	Description of Intervention	Principal confounders	Outcome data	Range of results	Adverse events	Lost to follow up	Probability value	Source population	Representative of population	Staff, place, facility	Subjects blind to intervention	Blind assessors	Data dredging	Same length of follow up	Appropriate Statistical tests	Compliance with the intervention	Accurate outcome measure	Control recruited same	Recruitment at same time	Randomised allocation	Concealed randomisation	Adjustment for confounders	Subjects lost to follow up	0-5	TOTAL
1	Bartolo et al. (2016)	1	1	1	1	2	1	1	1	1	0	1	0	1	0	0	1	0	1	1	1	1	1	0	0	0	1	0	19
2	Elliott et al. (2005)	1	1	1	1	1	1	1	1	0	1	0	0	0	0	0	1	1	1	0	1	0	0	0	0	0	0	0	12
3	Riberholt et al. (2013)	1	1	1	1	1	0	0	1	1	1	0	0	1	0	0	1	1	1	1	0	0	0	0	0	0	1	0	14
4	Toccolini et al. (2015)	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	1	1	1	1	1	0	0	0	0	0	1	0	19
5	Wilson et al. (2013)	1	1	1	1	0	1	1	0	1	1	0	0	0	0	0	1	1	0	0	1	0	0	0	0	0	1	0	12

Key (all except 5 principal co-founders)

Yes	1
No	0
Unable	0

Key (reporting 5)

Yes	2
No	0
Unable	0

Methodological quality of the included studies

In reviewing study quality, it is important to differentiate between the quality standards in a randomised controlled trial compared to a cohort and case-control studies. It is overly simplistic to assess different study designs in the same way (Hannan 2008: 211). Commonly, non-randomised studies can be broadly called observational studies as they do not randomise treatment but "observe" differences in outcomes that occur after treatment. This is important because well-designed observational studies are beneficial in assessing treatment efficacy. A study that compared 99 observational studies with randomised controlled trials found that observational studies yielded remarkedly similar results to those of randomised studies (Concato, Shah and Horwitz 2000: 1887). Indeed, these authors found that well-designed observational studies did not overestimate the outcome compared to randomised controlled trials (Concato, Shah and Horwitz 2000: 1890). In this systematised review, additional analysis was completed on observational studies using the Downs and Black checklist as it is has been tested and shown to be sensitive for non-randomised studies (Downs and Black 1998: 379). Although the vulnerability of non-randomised designs is different, many of the biases they seek to exclude are the same (Downs and Black 1998: 377). The quality of these studies depends on how well the study tests the association between the intervention and outcome. The next section will address if the non-randomised studies and randomised studies included are of sufficient quality to inform practice.

Study reporting

The reporting of the majority of randomised controlled trials was comprehensive enough to demonstrate appropriate study design to effectively assess consciousness. These studies described clearly their aim, main outcomes, characteristics of participants, possible confounders, main findings, important adverse events and the characteristics of those lost to follow up (Frazzatti et al. 2016; Krewer et al. 2015). Bartolo et al. (2016) and Toccolini et al. (2015) performed observational studies and reported all these key demographics. Taveggia et al. (2015) and Luther et al. (2008) described the

majority of these outcomes, however their results for consciousness were only described narratively. This is a limitation as it prevented analysis of the treatment effect of their results.

Riberholt et al. (2013) and Wilson et al. (2013) presented little statistical analysis by only giving an average percentage change. Elliott et al. (2005) and Greco et al. (2013) did not describe the participant characteristics or cofounders fully making it difficult to define their study population. Hence, there were limitations in the reporting of some of the observational studies making assessment of their findings incomplete.

External validity

The external validity defines whether causal relationships can be truly attributed to the measures, persons and settings used in the study (Steckler and McLeroy 2008: 9). The representative nature of the sample is highly important for external validity. For those in a PDOC, a representative sample can include traumatic and acquired aetiologies with a diagnosis of VS or MCS. Some authors have selected a subsection of these populations. For example, Greco et al. (2013: 6313) had a small sample of those in a MCS. This has high internal validity but poor external validity to a general PDOC population. Bartolo et al. (2016) also selected a subset of the population, those with a severe acquired brain injury and therefore were not representative of the whole population in PDOC.

Seven studies had good samples for external validity. Krewer et al. (2015) and Frazzitta et al. (2016) had a representative sample population of appropriate size. Toccolini et al. (2015: 655-656) and Riberholt et al. (2013: 1) also included a representative population but with a smaller sample size. Taveggia et al. (2015: 163), Elliott et al. (2005: 298-299) and Wilson et al. (2013: 476) had a small representative sample, but did not state where their participants were drawn from. As this is a difficult patient population to gain a representative sample from, many authors selected their patient population. This is problematic as when a sample size is small, representativeness is preserved, but the statistical power is compromised in terms of precision (Martínez-Mesa et al. 2014: 611-612). Consequently, these studies had low statistical power to determine treatment effect.

There was no reporting of the intervention provider in the majority of studies (Elliott et al. 2005; Greco et al. 2013; Riberholt et al. 2013; Wilson et al. 2013; Krewer et al. 2015; Taveggia et al. 2015;

Toccolini et al. 2015). Luther et al. (2008) stated therapists provided the standing intervention. Bartolo et al. (2016) states that participants were positioned in sitting or standing by a physiotherapist for 98% of the study but in one case a nurse performed the treatment. For Frazzitta et al. (2016) the treatment was provided by a physiotherapist with an intensive care nurse present. The reporting insufficiencies in many studies meant the efficacy of individual treatment providers is not possible to ascertain.

Internal Validity

Confounding factors distort the true relationship between treatment and effect therefore limiting the internal validity of studies (Rothman 2004: 295). For recovery of consciousness confounding factors are severity of injury, type of injury, age and comorbidities. For example, for the studies that included participants in the acute phase of recovery it is not possible to determine how much consciousness increased through natural recovery (Krewer et al. 2015; Frazzatti et al. 2016; Toccolini et al. 2015; Bartolo et al. 2016). Wilson et al. (2013) reported significant variation between participants in terms of time since their injury. This heterogenous study population threatens the internal validity of the study findings.

Two confounding factors affected Bartolo et al. (2016) which were the treatment selection process and uneven treatment and control groups. The researchers did not give any guidance to care providers as to who should be mobilised (Bartolo et al. 2016: 716). Treatment providers decided a third of patients were too seriously unwell to be positioned out of bed, so only the highest functioning patients were included in the mobilisation group (Bartolo et al. 2016: 720). This is a significant confounding factor, as patients with the least complex conditions would be expected to improve preferentially compared to those in a more critical condition. Treatment intensity varied between groups, for Bartolo et al. (2016: 716) mobilisation was sitting on the edge of the bed in a chair or on a tilt table. However, the non-mobilisation group was given the same amount of in-bed physiotherapy. Treatment intensity has been associated with improved functional outcomes (Kress 2009: 446). As the intensity of treatment in the mobilisation group was greater, functional improvements were more likely than in the non-mobilisation group.

Risk of bias of included studies

Allocation

Random allocation of a study population to either the treatment or control arm ensures the internal validity of a study by minimising bias (Fives 2013: 34). Randomisation ensures the differences observed between the study arms can be ascribed to the treatment as opposed to differences in the study population (Jüni, Altman and Egger 2001: 43). Random allocation was used in four studies with multiple arm trials, via computer-generated random sequence by a person not involved in enrolment (Frazzitta et al. 2016; Luther et al. 2008; Krewer et al. 2015; Taveggia et al. 2015). The remainder of the studies did not require random allocation as they had only one arm (Elliott et al. 2005; Greco et al. 2013; Wilson et al. 2013; Toccolini et al. 2015; Bartolo et al. 2016; Sibinelli et al. 2012). Allocation concealment was well executed in the papers that performed randomised trials.

Blinding

Blinding of assessors prevents detection bias which is crucial to ensure unbiased assessment of outcomes (Karanicolas, Farrokhyar and Bhandari 2009: 346). Un-blinded care providers can cause performance bias where additional treatment interventions can be provided preferentially to one group (Jüni, Altman and Egger 2001: 43). Performing a double-blind study was not possible for participants in these studies, as it is not feasible to offer sham or placebo standing interventions. Two higher quality studies completed blinded randomisation and assessor blinding (Frazzitta et al. 2016; Krewer et al. 2015). Three studies used un-blinded assessors and consequently had high detection bias (Elliott et al. 2005; Luther et al. 2008; Riberholt et al. 2013). Many studies did not provide sufficient information in their methods to show if the treatment provider or assessor were blinded (Greco et al. 2013; Toccolini et al. 2015; Sibinelli et al. 2012). Wilson et al. (2013) could not have the assessors blinded to the intervention, as they took the measurements in the three different positions for comparison, resulting in detection bias. Bartolo et al. (2016) also had high detection bias as they designed their study as a prospective observational study meaning all their assessors were not blinded. Taveggia et al. (2015) do not state if assessors were blinded but do say that statisticians were blinded

to the intervention. Overall, there was low risk of bias in only two of out of ten studies through adequate blinding of assessor and care providers (Frazzitta et al. 2016; Krewer et al. 2015).

Outcome assessment

The accuracy of the outcome assessment defines measurement bias. Study design should attempt to alleviate this through blinded assessment and a validated outcome measure. The majority of studies performed unblinded assessment of consciousness but used a valid outcome measure to do this (Elliott et al. 2005; Wilson et al. 2013; Bartolo et al. 2016; Toccolini et al. 2015; Luther et al. 2008). Unblinded assessment even with a valid outcome measure is problematic due to the subjective nature of neurobehavioral assessment scales.

Unvalidated assessment scales have been shown to give more significant treatment effects than validated scales (Marshall et al. 2000). Riberholt et al. (2013) used an unvalidated outcome measure; amount of time a participant had their eyes open. This causes problematic observer bias. This is similar to Greco et al. (2013) who performed a study analysing the changes in ElectroEncephaloGram ("EEG") and brain symmetry analysis between lying and standing. Previous studies in normal controls found EEG activities correlated with alertness (Chang et al. 2011). Greco et al. (2013: 6316) state that EEG activities in the β band are correlated with the working memory, but not necessary with alertness or arousal. Therefore, the use of an unvalidated outcome measure introduces threats to internal validity.

Incomplete outcome data

There were significant clinical imbalances in the mobilisation and non-mobilisation arm for the Bartolo et al. (2017) study but all participants were accounted for. The four studies which had two arms all showed low attrition bias (Frazzitta et al. 2016; Luther et al. 2008; Krewer et al. 2015; Taveggia et al. 2015).

Selective reporting

Two studies had high selective reporting bias as they picked the highest ranked behaviour over a week and compared this to baseline scores (Elliott et al. 2005; Wilson et al. 2013). In two other studies the neurobehavioral scale was compared descriptively not statistically (Luther et al. 2008; Taveggia et al. 2015). Riberholt et al. (2013) reported only a group average, which loses individual changes. Overall only four studies had a low risk of bias for selective outcome reporting (Frazzitta et al. 2016; Krewer et al. 2015; Toccolini et al. 2015).

Other potential sources of bias

Elliott et al. (2005) had an additional source of bias as it is not made clear what connection the un-blinded assessor had to the study team. Luther designed, recruited, performed the data collection and analysis, leaving little protection against personal bias (Luther et al. 2008). Riberholt et al. (2013) had two patients who were already aware which could have biased the results. Greco et al. (2013) and Wilson et al. (2013) did not give sufficient information to ascertain other sources of bias.

The studies by Taveggia et al. (2015) and Luther et al. (2008) were of medium quality, as both completed appropriate randomisation and allocation concealment. But their assessors were not blinded, and they only reported their consciousness results narratively. This is likely because Taveggia et al. (2015) and Luther et al. (2008) had consciousness as a secondary outcome measure. Toccolini et al. (2015) had a medium quality study, they reported all outcomes well but performed unblinded assessment. Bartolo et al. (2016) aimed to determine if early mobilisation of patients with severe acquired brain injury performed in intensive care influenced functional outcome. However, the selection of participants by care providers limits the validity of their findings making this a low-quality study (Bartolo et al. 2016). Riberholt et al. (2013) and Greco et al. (2013) performed low-quality studies due to their reporting biases and use of unvalidated assessment tools. However, for Riberholt et al. (2013) orthostatic hypotension was the main outcome measure making assessment of consciousness a secondary priority. Wilson et al. (2013) and Elliott et al. (2005) are low-quality studies as they had low external validity and high levels of bias. However, both of these studies were pilot studies. This is because, the newness of much of this research has limited the resources

available. This has reduced the ability for researchers to recruit larger population sizes and perform single blinding. However, two high quality studies did support the use of standing to increase consciousness. These were single blind randomised controlled trials by Frazzitta et al. (2016) and Krewer et al. (2015). Overall the majority of studies can be defined as medium to low quality due to difficulties with blinding of assessors, inadequate reporting and the use of unvalidated assessment measures.

Results of the included studies

Heterogeneity

Heterogeneity in a meta-analysis refers to the variation in study outcome between included articles (Higgins and Green 2011). Analysis of the studies included in this review showed diverse outcome measures, interventions and assessment. It was deemed that the clinical, methodological and heterogeneity was too high to perform a meta-analysis.

Methodological heterogeneity prevented meta-analysis for five reasons. The first being study design which can be divided into a single stand assessment or standing regimes. The differing study design meant that each author treated participants in different ways, making the combination of studies in a meta-analysis and sub-group-analysis imprudent (Russo 2007). Five single treatment studies were identified by the systematic search (Elliott et al. 2005; Greco et al. 2013; Luther et al. 2008; Wilson et al. 2013; Riberholt et al. 2013). The remaining five studies employed standing regimes of varying durations to improve consciousness and other outcomes (Frazzitta et al. 2016; Krewer et al. 2015; Taveggia et al. 2015; Bartolo et al. 2017; Toccolini et al. 2015). The decision to not perform a meta-analysis was informed by the diversity in study design.

A secondary reason for methodological heterogeneity was sample size, which differed significantly between trials. Bartolo et al. (2013) had the largest sample size of 102 participants and Greco et al. (2013) the smallest with only three participants. The majority of studies had 16 participants or fewer (Elliott et al. 2005; Luther et al. 2008; Taveggia et al. 2015; Wilson et al. 2013; Riberholt et al. 2013). The remainder of the studies had between 23 to 44 participants (Krewer et al. 2015; Frazzitta et al. 2016; Toccolini et al. 2015). Overall, there was a wide variety of sample size in the included papers.

The third contribution to heterogeneity was how the stand was achieved. Many researchers elevated their participants to increasing degrees with allocated time breaks between lying and standing. Taveggia et al. (2015) completed a change in tilt every ten minutes from 30° to 65° and then maintained this degree for 30-minutes. Whereas Greco et al. (2013) changed inclination every five minutes. Riberholt et al. (2013) gave specific guidelines going from 30°, 60° and 80° in 60-second intervals. Many authors took their participants up incrementally but did not state how long they took to do this (Elliott et al. 2005; Frazzitta et al. 2016; Krewer et al. 2015; Toccolini et al. 2015; Bartolo et al. 2017). Two authors took their participants up incrementally depending on patient adjustment, not on the time elapsed (Luther et al. 2008; Wilson et al. 2013). Observing patient adjustment reflects clinical practice most accurately. All articles varied greatly in the intricacies of their study design and most did not give enough information for reproducible methods.

The fourth contribution to methodological heterogeneity was treatment session duration. Elliott et al. (2005) performed a twenty-minute session. Whereas Luther et al. (2008) and Wilson et al. (2013) did not state a specific duration of treatment. Riberholt et al. (2013) performed a maximum of 18-minutes at 80° tilt angle. Single stand assessments were completed in approximately thirty minutes in the included studies.

For the standing regimes, Frazzitta et al. (2016) and Toccolini et al. (2015) conducted single daily sessions of standing for the duration of patient's intensive care stay. Whereas Krewer et al. (2015) performed ten sessions over a three-week period with an hour scheduled for treatment. Exact intervention timings were not given for Bartolo et al. (2017), although they had regular postural changes on average 52% of the time. There was significant variation between single treatment session and standing regimes.

The type of device was the final contribution to methodological heterogeneity. Standing was achieved via tilt table in five studies (Elliott et al. 2005; Wilson et al. 2013; Riberholt et al. 2013; Toccolini et al. 2015; Bartolo et al. 2017). Greco et al. (2013) used the ERIGO, a tilt table with integrated passive stepping only. Whereas four studies used the tilt table and ERIGO either as a control group or crossover design (Luther et al. 2008; Krewer et al. 2015; Frazzitta et al. 2016; Taveggia et al. 2015). There was greater variation in the ERIGO groups depending on the speed of the

integrated stepping, which differed between all studies. The varied use of devices produced significant heterogeneity in study design. Overall the methodological heterogeneity also prevented statistical meta-analysis, as a combination of results in this way would cause inaccurately high estimates of treatment effect (Fitzpatrick-Lewis et al. 2009: 6).

Clinical heterogeneity

Significant clinical heterogeneity existed between all studies, the main being the time since the injury occurred. Post brain injury the most significant improvements occur within the first six months (Tuel et al. 1992: 1). Three papers employed very early mobilisation within intensive care and it is not possible to ascertain what changes in consciousness occurred through natural recovery (Frazzitta et al. 2016; Bartolo et al. 2017; Toccolini et al. 2015). Other authors performed standing treatments within the first three months post-injury, at which time moderate to significant improvements can still be made (Luther et al. 2008; Krewer et al. 2015; Riberholt et al. 2013). The two papers that had the greatest variability within their study populations were Wilson et al. (2013) whose participants ranged from three months to 36 years, and Taveggia et al. (2015) whose participants ranged from three to 18 months post brain injury. Other articles did not state the time since the injury occurred (Luther et al. 2008; Greco et al. 2013). The disparity in the time since injury had occurred will cause variability in the data making it unacceptable for pooling.

Age is a strong prognostic factor for improvements post brain injury. Brain injury affects both young and mature groups which creates diverse study populations. The age of a person with TBI has been strongly associated with poorer outcomes, even accounting for other confounding outcomes such as surgical intervention (Dhandapani et al. 2012: 1). Some authors took care to stratify for age. Krewer et al. (2015) ensured no significant variation in age between study arms. On the other hand, Taveggia et al. (2015) had a variation of eight years in the experimental group but a much larger 16 years in the control group. The variation of age between participants in the included studies is a significant confounding factor.

The type of brain injury is another strong predictive factor of recovery. Those with an ABI have predominantly poorer recovery than those with a TBI (Hirschberg and Giacino 2011: 778). Frazzitta

et al. (2016) had a fairly even split between ABI and TBI, with the latter consisting of 64.5% of the study population. On the other hand, Bartolo et al. (2017) had 78.2% of the study population from a non-traumatic brain injury population. This could bias the outcome negatively in comparison to more evenly distributed studies. Significant heterogeneity was found between studies due to the different types of brain injury. This is problematic when there are inequalities in the severity of injuries between control and treatment groups. Taking everything into account, the diversity of clinically confounding factors between papers was too great to allow meta-analysis. Reporting the results in this way would have produced unreliable results for discussion.

In tables 4.5-6 the results of the studies as described by the authors and for the studies that provided original data the details of treatment effect. The original results are provided in the appendix 1.8 for comparison.

Table 4.5 Results of single stand studies

Study name	Sample Size	Author's interpretation of results	Secondary analysis
Elliott et al. (2005) (L. Elliott, M. Coleman, A. Shiel, B. Wilson, D Badwan, D. Menon, and J. Pickard)	**N = 12**	• 8 patients (3 VS and 5 MCS) showed improvements in the total number of behaviours and highest ranked behaviours. • 3 patients (2 VS and 1 MCS) demonstrated no change. • 1 MCS patient showed an increase in the highest ranked behaviour.	Cohen's d = 0.868 Relatively large treatment effect
Greco et al. (2013) (A. Greco, M.C. Carboncini, A. Virgillito, A. Lanatà, G. Valenza and E.P. Scilingo)	**N = 3**	• Significant improvement in Power Spectral Density and Brain Symmetry Index found in the β bandwidth. • These are correlated with the working memory.	Unable to calculate due to insufficient data.
Luther et al. (2008) (M. S Luther, C. Krewer, F. Müller and E. Koenig)	**N = 9**	• No significant change of consciousness was observed in the CRS-R. • No positive effect in consciousness found on either device.	Unable to calculate due to insufficient data.
Riberholt et al. (2013) (C. G. Riberholt, J. B. Thorlund, J. Mehlsen and A. M. Nordenbo)	**N = 16**	• During treatment, the average period that the patients had their eyes open was 9.5 minutes. • Average total intervention time was approximately 15 minutes. • Meaning that patients maintained their eyes open for an average 66% of the intervention period.	(Time with eyes open during treatment – time with eyes open before treatment) / time with eyes open before treatment x 100 = **percentage change of time with eyes open** (9.5 minutes – 7 minutes) / 7 x 100 = **35.71%**
Wilson et al. (2013) (B. A. Wilson, S. Dhamapurkar, C. Tunnard, P. Watson, and G. Florschutz)	**N = 16**	• **Sitting versus supine** 62.50% more behaviours for VS patients and MCS patients • **Standing versus supine** 75% more behaviours for VS patients and MCS patients	**Lying to sitting** Cohen's d = 0.367 (medium effect size) **Lying to standing** Cohen's d = 0.547 (medium effect size)

Description of effect sizes

Consciousness outcome after single treatment
A positive trend was demonstrated post analysis for all the majority of single treatment sessions. Elliott et al. (2005) showed a relatively large treatment effect when using a tilt table to increase consciousness. Wilson et al. (2013) found a medium effect size between lying and sitting and lying and standing on a tilt table. Although standing produced a larger treatment effect compared to sitting. Riberholt et al. (2013) used the duration of time the participants had their eyes open to show increased levels of arousal, for which they spent 35.71% more time with their eyes open.

Table 4.6 Results of standing regime studies

Study name	Sample Size	Author's interpretation of results	Secondary analysis (treatment group)	Secondary analysis (control group)
Bartolo et al. (2016) (M. Bartolo, S. Bargellesi, C. A. Castioni, D. Intiso, A. Fontana, M. Copetti, F. Scarponi, D. Bonaiuti)	**N = 102**	• A statistically significant improvement in patients' GCS and LCF scores when comparing admission-discharge values.	**Mobilisation group** GCS post treatment - GCS prior to treatment) / GCS prior to treatment x 100 = (10.3 - 7.3) / 7.3 x 100 = **41.09% change**	**Non-mobilisation group** (GCS post treatment - GCS prior to treatment) / GCS prior to treatment x 100 = (7.3 - 5.7) / 5.7 x 100 = **28.07% change**
Frazzitta et al. (2016) (G. Frazzitta, I. Zivi, R. Valsecchi' S. Bonin, S. Maffia, K. Molatore, L. Sebastianelli, A. Zarucchi, D. Matteri, G. Ercoli, R. Maestri and L. Saltuari)	**N = 31**	• At discharge from ICU the control group and treatment group showed a significant improvement in GCS, DRS, CRS-R, LCF. • However early stepping verticalization improved the CRS-R score to a greater extent.	Cohen's d = 2.300 (large treatment effect)	Cohen's d = 1.996 (large treatment effect)
Krewer et al. (2015) (C. Krewer, M. Luther, E. Koenig, F. Müller)	**N = 44**	• ERIGO group improved by a median of 2 points on the CRS-R. • Tilt table group improved by a median of 5 points on the CRS-R.	ERIGO Cohen's d = 0.180 (small treatment effect)	Tilt table Cohen's d = 1.934 (large treatment effect)
Taveggia et al. (2015) (G. Taveggia, I. Ragusa, V. Trani, D. Cuva, C. Angeretti, M. Fontanella, P. Paolo Panciani and A. Borboni)	**N = 12**	• CRS and LCF scores before and after treatment demonstrated no change for both groups.	Unable to calculate due to insufficient data.	Unable to calculate due to insufficient data.
Toccolini et al. (2015) (B. F. Toccolini, E. Fernanda Osaku, C. Rejane Lima de Macedo Costa, S. Nogueira Teixeira, N. Lamberti Costa, M. Fernanda Cândia, M. Aparecida Leite, C. Eduardo de Albuquerque, A. Cezar Jorge and P. A. Delfino Duarte)	**N = 23**	• GCS significantly improved between first and last day at 30°, 45° and 60°.	**Mobilisation at 60°** (GCS post treatment - GCS prior to treatment) / GCS prior to treatment x 100 = (8.1 - 5.5) / 5.5 x 100 = **47.37% change**	**N/A**

Consciousness outcome after treatment regime

Frazzitta et al. (2016) showed a large treatment effect compared to the control group using an ERIGO tilt table to increase consciousness. However, this is in contrast to Krewer et al. (2015) who found only a small treatment effect on the ERIGO tilt table, but a large effect for the traditional tilt table. Percentage increases were demonstrated after early mobilisation in intensive care on a tilt table in two Italian studies (Bartolo et al. 2016; Toccolini et al. 2015). Treatment regimens showed broadly positive trends but on differing devices and with different protocols.

For three studies it was impossible to ascertain treatment effect or percentage change. Greco et al. (2013) performed a single stand study using EEG power spectral analysis and symmetry index pre and post inclination. The complexity of the data produced by this study did not allow treatment effect to be calculated. For Luther et al. (2008) there was insufficient data available in changes on CRS-R in this study to perform statistical analysis. Taveggia et al. (2015) state no difference was found in GCS or LCF before and after treatment but do not give data for analysis.

Adverse events

Five studies described their adverse events (Elliott et al. 2005; Frazzitta et al. 2016; Greco et al. 2013; Wilson et al. 2013; Bartolo et al. 2016). The most common event was discontinuation of standing treatment due to orthostatic hypotension. This is a sudden drop in blood pressure when a person assumes a standing position (National Institute of Neurological Disorders and Stroke 2018). Luther et al. (2008) had only one interruption on the ERIGO, whereas, for the conventional tilt table six patients displayed problems. Krewer et al. (2015) had an average therapy time of two minutes more on the ERIGO compared to the tilt table, this statistically significant difference between treatment times was due to increased discontinuation on the tilt table. This is consistent with Taveggia et al. (2015) for whom three out of four ERIGO participants managed to complete the treatment without interruption, however only one of the tilt table group completed it without disruption. Toccolini et al. (2015) found that the amount of hypotension reduced over time, incidence on the first and second day was common, but no incidents occurred on last day before discharge from intensive care. For Riberholt et al. (2013) only one patient managed to complete 20

minutes in a standing position and on average treatment had to be discontinued after 4 minutes and 30 seconds. Discontinuation of treatment was commonplace in tilt table treatment but infrequent on the ERIGO.

Chapter 5: Discussion

The objective to be tested was the effect of single standing treatment or assisted standing regimes on consciousness for individuals in a PDOC. Ten papers were found, two of high quality, but the majority medium to low quality. These have still provided some helpful insights on the use of standing to mediate consciousness. This discussion will address standing's effect on consciousness, types of standing device, timing of rehabilitation, study design in rehabilitation medicine, sample size, assessment methods, quality of included literature. It will assess the strengths and limitations of this review, present conclusions and discuss the implications for practice and future research.

Standing's effect on consciousness

The best evidence supports standing regimes' ability to enhance consciousness. The single stand studies were of lower quality and do not give the same standard of evidence. Frazzatti et al. (2016) and Krewer et al. (2015) performed the two highest quality randomised controlled trials that showed standing had a high treatment effect on consciousness. These results can be used to support standing regimes' effect because they were rigorously controlled. The two Italian intensive care studies also supported standing regimes' effectiveness, but their results should be viewed with greater caution (Bartolo et al. 2016; Toccolini et al. 2015). Toccolini et al. (2015) support the use of standing regimes, but had no control group, so it is not known how much natural recovery improved consciousness. The results from Bartolo et al. (2016) should be viewed with major reservations due to the imbalances between the mobilisation and non-mobilisation groups.

Single stand studies did show a positive improvement in consciousness for all studies (Elliott et al. 2005; Wilson et al. 2013; Riberholt et al. 2013; Greco et al. 2013; Luther et al. 2008). The quality of the studies was not as high as that of the studies investigating treatment regimes. All of the single stand studies contained biases in either reporting, blinding or choice of outcome measure. Overall, the quality of evidence is higher for standing regimes than single stand studies.

Types of standing device

The type of standing device to best affect consciousness is more difficult to ascertain. Three studies directly compared the tilt table with the ERIGO, a standing device with integrated stepping

(Krewer et al. 2015; Luther et al. 2008; Taveggia et al. 2015). The ERIGO was found to increase the duration of treatment time and reduced discontinuations due to orthostatic hypotension. Luther et al. (2008) performed a single stand study and Taveggia et al. (2015) a standing regime, both comparing the ERIGO with the tilt table. Neither author found a preferential improvement in consciousness on either device. However, both found reductions in the most common adverse event. With the ERIGO group, Luther et al. (2008), stated only one discontinuation whereas six patients had orthostatic hypotension on the tilt table. Taveggia et al. (2015) also found that haemodynamically unstable patients had a reduction in orthostatic hypotension on an ERIGO.

Krewer et al. (2015) was the only study that found a difference in consciousness between the two devices. This study found a large treatment effect on the tilt table, but only a small treatment effect size on the ERIGO (Krewer et al. 2015: 10). This was despite ten members of the tilt table group having a potentially poorer prognosis (Krewer et al. 2015: 11). In addition to this, the tilt table group had two-minutes fewer net therapy time compared to the ERIGO group due to adverse events (Krewer et al. 2015: 11). This statistically significant difference did not create a clinical difference (Krewer et al. 2015: 11). This would suggest that regular treatments are more important than a longer treatment duration, although further studies are required to confirm this hypothesis. Krewer et al. (2015: 11) postulate that as persons in disorders of consciousness have slowed sensory processing the ERIGO could have caused over-stimulation which reduced treatment effect. Indeed, only one study found a more positive treatment effect on the tilt table compared to ERIGO. An alternative explanation is that the occurrence of orthostatic hypotension on the tilt table caused an increase consciousness. This warrants further research. From a clinical perspective using an ERIGO may increase treatment time but it may not affect consciousness as effectively as the tilt table. Therapists will need to base device decisions around the individual patient's condition and treatment goals.

Timing of rehabilitation

It is important to consider the optimal time to start standing interventions to improve consciousness. Consciousness has been shown to improve through early mobilisation in intensive care by Frazzitta et al. (2016) and by Bartolo et al. (2016). Frazzitta et al. (2016) found that standing on an ERIGO created significant improvements in consciousness compared to traditional physiotherapy. Bartolo et

al. (2016) found improvements in consciousness via mobilisation into sitting or standing compared to a non-mobilised control group. However, for Bartolo et al. (2016), the imbalance in clinical severity between their treatment and control group weakens the legitimacy of their results. Toccolini et al. (2015) performed a medium quality study which found improvements in consciousness from day one to discharge in intensive care unit. These authors also found improvements in consciousness correlated to the amplitude of standing, more behaviours were demonstrated at 90° compared to 30°. The difference in consciousness at higher degrees is an interesting finding, but could be due to the increased time in standing. Further research is required if greater degrees of standing is to be used in very early rehabilitation. The diverse quality of studies does not make it possible to say if standing in acute settings can increase consciousness.

Two studies in the sub-acute rehabilitation phase used standing regimes (Taveggia et al. 2015; Krewer et al. 2015). Taveggia et al. (2015) performed a medium quality study which found no difference in consciousness before and after a standing regime. Krewer et al. (2015) found a positive treatment effect for both the tilt table and the ERIGO. Three other authors completed single stands in the sub-acute rehabilitation phase (Luther et al. 2008; Riberholt et al. 2013; Greco et al. 2013). Luther et al. (2008) state no significant change of consciousness was observed. On the other hand, Riberholt et al. (2013) and Greco et al. (2013) report improvements in consciousness, but used unvalidated assessment tools. Krewer et al. (2015) provide the only strong evidential support for standing improving consciousness for persons in sub-acute rehabilitation. Overall the current evidence base is not strong enough to recommend an appropriate time to initiate standing treatment.

Study design in this area of rehab medicine

The use of randomised controlled trials with this patient group provided some of the strongest evidence to support standing regimes. Randomised controlled trials are widely heralded as the gold standard because they provide the best evidence of treatment effect, but they are difficult to implement in rehabilitation research (Sackett et al. 1996: 72). Primarily this is because a true control group is not possible in this population. In addition, standing is part of traditional treatment in the sub-acute setting; so randomising patients to a control group prevents them from receiving normal care. The randomised controlled studies in this review managed to generate control groups by comparing

different devices or having a non-mobilisation group in intensive care. It is often not possible to provide a meaningful control group for standing treatments in sub-acute centres (Barnett et al. 2012: 176). Most interventions in rehabilitation settings are highly individualised and a control group comparison is not reasonable (Dijkers 2009: 5). Another complexity of rehabilitation research is that intervention may consist of much more difficult to measure entities. For example, the individual therapist's manual handling of a participant will vary among practitioners. Controlling for these individualised treatment programmes is not possible in a typical rehabilitation setting. Blinding was a problem in the majority of included studies which is a central tenet of randomised controlled trials. However, for a rehabilitation treatment, such as standing, blinding of treatment providers and patients is not possible (Dijkers 2009: 5).

Researchers need to ask if traditional randomised and blinded studies are the best way to answer these research questions, or if a non-randomised study design could give more meaningful results in this study area. This would reduce the requirement to control confounding factors that are uncontrollable in this area of research. Many varied interventions will affect consciousness which cannot be withdrawn for ethical reasons. These include nursing interventions, occupational therapy, drug treatments, interactions with family members and regular positioning. Even if all patients are given these interventions, the proportions in which they are given will vary. Mostly the research papers do not record the other treatments in detail which makes them impossible to quantify. In addition to this when regular physiotherapy is on-going it is unethical to withhold regular positioning. Even sitting has a positive effect on consciousness (Wilson et al. 2013). Diversifying study designs in rehabilitation research can create more realistic research scenarios to answer clinical questions.

The focus on using the most controlled research designs may steer researchers away from finding the research design that best answers their research question (Dijkers 2009: 1). So, it is important to consider other types of research design in order to truly answer the research in a way that will reflect clinical practice. The types of study design that may better answer this research question will be addressed in the implications for research section.

Variability of study design

The variability in study design has limited the potential for concrete conclusions to be made regarding the best type of standing device and best treatment method to increase consciousness. Single stand assessment or standing regimes were the main design differences. The method of standing also varied between studies; most used a tilt table or a fully supportive standing device with integrated stepping (ERIGO). The method used to take a person into standing varied between studies, many studies took patients into standing using set time intervals (Taveggia et al. 2015; Greco et al. 2013; Elliott et al. 2005; Frazzitta et al. 2016; Krewer et al. 2015; Toccolini et al. 2015; Bartolo et al. 2017; Riberholt et al. 2013). Only two studies took participants into higher degrees as patients adjusted (Luther et al. 2008; Wilson et al. 2013). This is of clinical significance, because the studies who took participants up on the basis of time and not patient adjustment could have increased the incidence of orthostatic hypotension. There is not sufficient evidence to state if certain types of standing device or durations of treatment enhance consciousness. Suggestions on optimal standing duration are not necessary for those in PDOC due to their complexity and lack of homogeneity. However further research is warranted as to the best method of standing those in disorders of consciousness to reduce incidences of orthostatic hypotension while still improving consciousness.

A homogenous study population ensures that treatment effect is attributed to the intervention and not to other factors such as age or severity of injury (Spieth et al. 2016: 1343). The internal validity of clinical trials is directly related to having even participant characteristics in the control and treatment arms (Spieth et al. 2016: 1343). The internal validity of Frazzitta et al. (2016: 7) was compromised through uneven comparator arms; the control group were higher in age and the number of participants with haemorrhage was greater. Krewer et al. (2015: 10) did not have statistical differences for factors shown to be predictive in terms of outcome, but did have ten participants with a potentially more severe diagnosis in the control group. However, despite this, the tilt table control group improved more than the ERIGO treatment group. Taveggia et al. (2015: 164) and Luther et al. (2008: 1038) had higher variation in age in the control group compared to the intervention group. This is important to note as age is a strong prognostic factor for improvements post brain injury (Dhandapani et al. 2012). For these four studies with two arms, there were uneven sample characteristics which could have

biased the results. Rehabilitation studies that choose to use a randomised controlled method need to have no underlying differences in baseline participant characteristics between treatment and control arms, as this ensures that the effect size can be attributed to the treatment and not to uneven sample demographics.

Sample size

Sample size is important in research that seeks to examine the efficacy of a treatment via hypothesis testing (Biau, Kernéis and Porcher 2008: 2282). In order to gain an adequate sample size, a power calculation is essential (Biau, Kernéis and Porcher 2008: 2282). Two randomised controlled trials addressed power calculations. Krewer et al. (2015: 3) completed a power calculation a priori and recruited to protect for potential dropouts. Frazzitta et al. (2016: 5) did not complete a power calculation as they stated it was not feasible and not necessary as it was a pilot study. Inadequately powered studies may not be sufficiently powered to detect between-group differences and the study may be falsely negative leading to a type II error (Nayak 2010: 469). Appropriately powered studies improve their statistical power which is needed to evaluate treatment effect.

Calculation of sample size in non-randomised trials is a complex issue. The decision to include case series and cohort studies in this systematised review means that these will not have needed to be powered to detect between-group differences. Other researchers have proposed formulae to calculate sample size in a self-controlled case series (Musonda, Farrington and Whitaker 2006). These calculations assume for example that the incidence of adverse events is constant (Musonda, Farrington and Whitaker 2006: 3). As adverse events in this population cannot be assumed to be constant there is still no verifiable method to calculate sample sizes for a case series methodology which uses complex participants. Indeed, the underlying heterogeneity in rehabilitation research means it can be difficult to accurately calculate sample sizes.

For many of the included studies in this systematised review, it was not possible to calculate a sample size that would detect pre- and post-treatment differences due to the many underlying variables. Seven out of the ten studies did not discuss a power calculation and these studies had small sample sizes with 31 participants or fewer (Frazzitta et al. 2016; Toccolini et al. 2015; Elliott et al. 2005; Luther et al. 2008; Taveggia et al. 2015; Wilson et al. 2017; Riberholt et al. 2013). Bartolo et al.

(2013: 716) recruited 102 participants. These authors state that each participating centre was asked to enrol at least ten patients, but gave no reasons for this number. It is not necessarily a flaw in the methods of non-randomised studies avoid using a power calculation. However, it does aid transparency and accurate reporting if the reason for not completing one is stated. The method to calculate sample sizes in non-randomised trials warrants further research in order to support accurate reporting.

Assessment method

All good research requires outcome measures that are valid, reliable and sensitive. The validity of the assessment method was crucial in all of these studies due to the subjective nature of neurobehavioral tools to measure consciousness and the lack of alternate diagnostic confirmation. For a neurobehavioral tool, the internal consistency is most important, as this determines how well it differentiates between different states of consciousness. A systematic review found the CRS-R best-evaluated consciousness and could be used with only minor reservations (Seel et al. 2010: 1796). For future research, this should be the neurobehavioral tool of choice to differentiate between consciousness states. In this systematised review, three articles used the CRS-R (Luther et al. 2008; Krewer et al. 2015; Taveggia et al. 2015). Other authors used outcome measures with less specificity, such as the GCS which has been shown to have a limited ability to differentiate between vegetative and minimally conscious states (Schnakers et al. 2009). Three studies utilised GCS as an outcome which has poor internal reliability to assess consciousness (Frazzitta et al. 2016; Bartolo et al. 2016; Toccolini et al. 2015). Frazzitta et al. (2016) qualified these findings appropriately through using the CRS-R as well, which has excellent content validity (Seel et al. 2010: 1805). Bartolo et al. (2016) also used other outcome measures but these have not been validated to assess consciousness. As their neurobehavioral tool Elliott et al. (2005) and Wilson et al. (2013) used the WHIM to assess consciousness level. The WHIM has good content validity but unproven criterion validity (the extent to which it measures consciousness) has not been accurately determined (Seel et al. 2010: 1806).

However, other studies did not use outcome measures that were appropriate or valid. Riberholt et al. (2013) chose to measure consciousness as the duration of time participants spent with their eyes open. Other neurobehavioral tools record eye opening as a consciousness measure (e.g. WHIM, CRS-

R). However, other authors have stated duration of eye-opening is insufficient to assess active brainstem function, as patients in a vegetative state can have their eyes open but remain unaware of their environment (Majerus et al. 2005: 408). For persons in disorders of consciousness, an increased amount of time with their eyes open could indicate improvements in arousal but not true increases in consciousness. Hence duration of eye-opening is not a valid neurobehavioral assessment. Greco et al. (2013) used EEG activity which they state correlates with alertness. However, the utility of this as a diagnostic tool has yet to be fully validated. Young (2000: 482) states that it is not reliable for differentiating between conscious and unconscious brain processing. Hence there were some insufficiencies in the neurobehavioral tools chosen. The results of Greco et al. (2013) and Riberholt et al. (2013) should be viewed with some caution as the tools they employed cannot be reliably shown to measure consciousness.

Quality of included studies

The conclusions of this review are limited by the quality of the studies available for inclusion. The overall risk of bias was unclear for eight studies (Elliott et al. 2005; Greco et al. 2013; Taveggia et al. 2015; Luther et al. 2008; Wilson et al. 2013; Bartolo et al. 2016; Toccolini et al. 2015; Riberholt et al. 2013). Appropriate blinding was a problem in half of the included studies (Elliott et al. 2005; Luther et al. 2008; Wilson et al. 2013; Taveggia et al. 2015; Bartolo et al. 2016). Blinding is notoriously difficult in trials that involve physical interventions, particularly where the participant experiences sensations during the intervention (Page and Persch 2013: 158-159). However, it is possible for one person to perform the intervention and another to perform the assessment in order for single blinding to be achieved (Page and Persch 2013: 158). Frazzitta et al. (2016) and Krewer et al. (2015) achieved single-blind studies in this way, as the data collector was blinded to group assignment and treatment (Page and Persch 2013: 158). Blinding of assessors is important to avoid detection bias which is particularly relevant when outcomes, like the neurobehavioral tools used, are subjective (Hróbjartsson et al. 2012: 2). Elliott et al. (2005) and Luther et al. (2008) performed an unblinded assessment of consciousness which creates the high potential for detection bias and consequently limits the objectivity of these results (Karanicolas, Farrokhyar and Bhandari 2009: 346). Although the lack of blinding did not necessarily show a positive bias, since Luther et al. (2008) found no difference in

consciousness after a single stand assessment. Inadequate blinding of assessors was a primary source of bias in the included studies.

The lack of original data provided by the studies limited statistical analysis. Firstly, the lack of available data made it impossible to do a sub-group analysis to fully assess heterogeneity (Higgins and Green 2011). Subgroup analysis is beneficial in order to look for effective modifiers.

In this systematised review, it would have been beneficial to compare single stands with standing regimes. However, it was statistically imprudent to complete a subgroup analysis due to the low number of studies available which makes the likelihood of false positives too high (Burke et al. 2015: 1-5). Secondly, insufficient original outcome data was provided by the studies to allow calculation of Cohen's d treatment effect. Percentage-change was the only possible calculation, which has low statistical power to detect treatment effect (Vickers 2001: 5). In addition to this, it is not possible to directly compare percentage change with the true Cohen's d calculation of treatment effect. This reduced the statistical comparison between studies. Overall, the statistical analysis was complicated by the low number of studies retrieved and the inability to access raw data.

Systematised review limitations

A potential inadequacy of this review was that data extraction was only completed by one researcher (HN). Previous research has shown that more errors occur with single data extraction compared to double data extraction (Buscemi et al. 2006). In this review, every effort was made to objectively follow the Cochrane data collection form and Downs and Black checklist. When uncertainties arouse in data collection these were checked with the second reviewer (AK). However, single data extraction has not been found to significantly affect treatment effect (Buscemi et al. 2006: 100). Following the data extraction forms guidance will have minimised errors but unconscious bias cannot be ruled out. The Cochrane data collection form was chosen for its assessment of methodological quality and risk of bias. However, the Cochrane Risk of Bias tool (2014) which is embedded within the data collection form has been criticised by multiple authors for its lack of detailed guidance, over-sensitivity and low inter-rater agreement (Armijo-Olivo et al. 2014; Jørgensen et al. 2016). Good consensus ratings are crucial to ensure accurate bias reporting, hence, the use of the Cochrane Risk of bias tool (2014) is a limitation. The Downs and Black checklist (1998) was used as

an additional assessment for the included observational studies. Downs and Black was selected for its good test-retest and inter-rater reliability, high internal consistency, and good criterion and face validity (Downs and Black 1998: 380). Although every effort has been made to ensure unbiased reporting, the main limitation of this systematised review is the single data collection process.

Another limitation of this systematised review was the database search. The search was comprehensive, but problematical, due to the main search terms not being registered as keywords in databases. The inclusion criteria for this review required the population to be in a defined state of consciousness which improved specificity. However, it also complicated the search terms. Although no language settings were put in place, no relevant foreign language papers were identified, this could be due to the terminology used in the search. This may have limited the number of studies that were retrieved. In addition to this, terms like "stand" create a high amount of unrelated citations which are difficult to refine. Therefore, the search strategy was robust, but the lack of registered keywords may have caused difficulty in retrieving primary papers.

Systematised review strengths

This review establishes the current evidence for the effect of standing on consciousness. It is the first systematised review to assess this treatment and outcome. The strengths of the review process are the rigorous literature search and reporting following the PRISMA-P protocol (Liberati et al. 2009). The inclusion and exclusion criteria identified disorders of consciousness, which enabled specificity in the assessment of those in a PDOC. Another positive of this review is the transparent reporting of the studies identified. This includes the data extraction process using two types of data collection form (Cochrane data collection 2014; Downs and Black 1998). This allowed the nuances of randomised controlled trials and observational studies to be assessed differently. Full statistical analysis of the included articles was not possible but rigorous assessment of the studies was made to come to this conclusion. The narrative analysis had a clinical focus, which enabled treatment focused conclusions to be made. This was a rigorously conducted systematised review which was sensitive to clinical considerations.

Implications for practice

The two highest quality studies that provide some evidence to support the use of standing to increase consciousness (Frazzitta et al. 2016; Krewer et al. 2015). These studies do not have many vital study or sample characteristics in common. Frazzitta et al. (2016: 4) included participants between three to 30 days from their acquired brain injury and completed treatment on an ERIGO. Krewer et al. (2015: 2) found the greatest effects on the tilt table and participants were four weeks to six months post-injury. However, further evidence is needed if standing treatments are to continue to be part of normal practice.

Treatment providers may be seeking protocol guidance on treatment implementation time and optimal treatment duration. Other authors have given protocol suggestions for home-based standing programmes to improve functional outcomes such as lower limb range of movement (Paleg and Livingstone 2015). There is insufficient evidence to give such guidance. Indeed, with the complexity of patients who are in disorders of consciousness, it is imprudent to give strict guidance. Therapists need to tailor their individual standing treatments to the needs of the person in a PDOC.

The evidence base supports the safe use of standing regimes in acute and rehabilitation settings for individuals without major complications. For persons with lower limb fractures, unstable intracranial pressure, critically low bone mineral density or pressure sores it is not advisable to use a tilt table. But if these risks are resolved and agreement of the multidisciplinary team is reached, then standing trials can commence.

An on-going difficulty in positioning individuals in PDOC is the consistent drops in blood pressure that cause discontinuation of treatment. The use of a tilt table with integrated stepping has been evidenced to reduce the occurrence of orthostatic hypotension (Krewer et al. 2015: 10; Luther et al. 2008: 1039; Taveggia et al. 2015: 165). Taveggia et al. (2015: 165) divided their participants into haemodynamically unstable and stable, and these authors found that passive leg movements reduced orthostatic hypotension in those who were unstable. Using an ERIGO or another standing device with integrated stepping is a method to reduce the occurrence of orthostatic hypotension.

Implications for research

In the main discussion, it was highlighted that randomised controlled trials may not be best suited to answer questions in specialist individualised research. The answer to this, a rigorous but different method is needed. Multiple single-case designs exist that are true experimental designs which test treatment effects (Barnett et al. 2012: 178). To assess how standing affects consciousness an ABAB design would be beneficial. In this study design a baseline phase is followed by a treatment phase and then both phases are repeated. If changes in consciousness occur during the treatment phase it can be assigned to the treatment and not to other factors. Measurements need to be taken over a pre-defined time period (Barnett et al. 2012: 178). The logic of this study design is that if the predicted change occurs reliably at the point of the intervention, then changes can be credited to the treatment (Barnett et al. 2012: 178). From a real-world clinical perspective, this removes the need to control compounding factors; such as natural recovery and other therapies provided in the rehabilitation setting. Indeed, removing the effects of other therapies is unnecessary as this would not occur in clinical practice. Therefore, using an ABAB study design means the intervention is the independent variable and improvements in the treatment phase can be attributed to treatment effect.

The systematic measurement of consciousness and structured implementation of standing regimes can be compared amongst individuals using an ABAB study design. Comprehensive reporting of the underlying study characteristics is essential for this. In addition to this, it should be completed in a single-blinded manner to allow for objective measurement of consciousness using a valid neurobehavioral tool such as the CRS-R. As the optimal time to start treatment is of interest to standing treatment providers. The ABAB study could be implemented in acute and sub-acute rehabilitation settings. Therefore, an ABAB study would allow the effectiveness of the treatment to be analysed without the need for a specific control group and reduce the danger of confusion through compounding factors.

Patient and public involvement will be central to improving the above-proposed study at all stages of the project. Semi-structured interviews were started in order to set the priorities of the research and inform the research question. The Silver Linings group had specific opinions about standing treatments to improve consciousness, some suggested that we need to understand its potential benefits

especially as it could greatly change patient's lives if it is beneficial. Others had thoughts on the rehabilitation process stating better is recovery is made when you start physiotherapy earlier. The design of the research project will continue to be discussed through semi-structured interviews at the two brain injury charities (Headway and Silver Linings) and a hospital patient forum. The patient forum has agreed to assist with planning and analysing the conduct of the research project. This will include practice of consent procedures and reading all documentation to check for readability. After the statistical analysis of the study, the results will be anonymised and verbally presented to each charity and the patient forum. Finally, members of the charities and the patient forum will be informed of the outcomes of the research in the form of a presentation at each of the group meetings. Hence, patient and public involvement will be embedded in the design and conduct of this on-going research project.

To enhance the understanding of the potential causes of standing treatment's effect on consciousness a mixed methods approach could be used. This would give greater understanding through qualitative observations of those providing the treatment and quantitative measurements of consciousness. The qualitative assessment could involve observation of a treatment session of passive standing. This would involve systematic and detailed observations by an assessor of all behaviour and conversation performed by the therapists. In addition to this, the method of standing that is employed for that participant could be recorded. The quantitative neurobehavioral observations would need to be conducted by a blinded assessor pre and immediately post the standing treatment session. Consistent changes in consciousness post-treatment would demonstrate treatment efficacy. The use of mixed methods would give more meaningful insights into the potential causes of fluctuations in consciousness. This study would assess if there is any correlation between the actions of standing treatment providers and changes in consciousness. Hence diversity in study design will help provide richer analysis into the potential efficacy of standing treatments.

Conclusion

This review cannot be directly compared as it is the first of its kind, but it has much in common with previous systematic reviews on standing. These were the complexities in the literature search, the variability in use of outcome measures, the heterogeneity of the included literature and the overall

quality of studies (Newman and Barker 2012: 1074; Paleg and Livingstone 2015: 13). This review has specifically analysed the effect of standing on consciousness for those in PDOC. This is an essential question that needs answering, as standing treatments are commonly used to treat consciousness, but no systematised assessment has been made of their efficacy (Chang et al. 2004; Moore and Jones 2011).

Hence, the intention of this systematised review was to look at the efficacy of standing treatments to remediate consciousness for those in PDOC. Efficacy means that the treatment does more good than harm in ideal conditions (Cochrane 1972: 26-35). There was limited high-quality evidence to support the efficacy of standing treatments to improve consciousness for those in PDOC. The majority of studies found a positive treatment effect. Overall, eight out of ten studies showed an improvement in consciousness in a standing position. An increase in consciousness was found in early mobilisation studies in intensive care by two medium quality Italian studies (Bartolo et al. 2016; Toccolini et al. 2015). Increases in consciousness were also found in sub-acute rehabilitation settings (Taveggia et al. 2015; Krewer et al. 2015). There is support from multiple single stand observational studies, but these are of low quality (Elliott et al. 2005; Wilson et al. 2013; Riberholt et al. 2013). Frazzitta et al. (2016) and Krewer et al. (2015) performed the two highest quality studies and these showed high treatment effects with standing regimes. However, the overall quality of evidence is poor and two high-quality studies are not enough to state that standing is an effective treatment method for those in a PDOC.

The main recommendation that can be made is that the ERIGO reduces the number of discontinuations due to orthostatic hypotension. The second recommendation that can be made is the use of mixed methods research to generate a deeper understanding of passive standing treatment efficacy. As this would provide an understanding of how treatment providers actions affect consciousness for passive standing treatments. However, no definitive recommendations can be made on the ability of passive standing to mediate consciousness for those in a PDOC; as the quality of rehabilitation research was generally poor due to insufficient blinding and selective outcome measure reporting. In conclusion, there is limited high-quality evidence to support the use of standing to improve consciousness for those in a PDOC (Frazzitta et al. 2016; Krewer et al. 2015). The question

of how best to therapeutically rehabilitate those in disorders of consciousness continues to warrant further research.

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Appendix 1.0

Glossary of key terms

Acquired Brain Injury	ABI
Coma recovery scale-revised	CRS-R
Central thalamic deep brain stimulation	CT-DBS
Disorders of Consciousness Scale	DOCS
Disability rating scale	DRS
ElectroEncephaloGram	EEG
Early Rehabilitation Barthel Index	ERBI
EThOS	e-theses online service
Tradename – for a fully supportive standing device with integrated stepping	ERIGO
Fluorodeoxyglucose positron emission tomography	FDG-PET
Glasgow outcome scale	*GOS*
Glasgow coma scale	*GCS*
Prolonged disorder of consciousness	PDOC
Levels of cognitive function	LCF
Minimally Conscious State	MCS
Sensory Modality Assessment Technique	SMART
Sensory Tool to Assess Responsiveness	STAR
Traumatic Brain Injury	TBI
United Kingdom	UK
Vegetative State	VS
Wessex Head Injury Matrix	WHIM
Western Neuro Sensory Stimulation Profile	WNSSP

Appendix 1.1 PRISMA-P format

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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review
Update	1b	If the protocol is for an update of a previous systematic review, identify as such
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments
Support:		
Sources	5a	Indicate sources of financial or other support for the review
Sponsor	5b	Provide name for the review funder and/or sponsor
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage

Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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Appendix 1.2 Search strategy including hits

CINAHL 24/2/18

Number	PICO	Search term and Field	Hits
S1	Population A Aetiology Vascular event	(MH "Nervous System Diseases") OR (TI "Nervous system diseases") OR (AB "Nervous System Diseases") OR (MH "Central Nervous System Diseases") OR (TI "Central Nervous System Diseases") OR (AB "Central Nervous System Diseases") OR (MH "Brain Diseases") OR (TI ""Brain Diseases") OR (AB "Brain Diseases")	13,253
S2		(MM "Cerebrovascular Disorders+") Here the subject heading has been explored to contain narrower and more explicit terms including "Basal Ganglia Cerebrovascular Disease" OR "Carotid Artery Diseases" OR "Cerebral Ischemia" OR "Cerebral Small Vessel Diseases" OR "Cerebral Vasospasm" OR "Intracranial Arterial Diseases" OR "Intracranial Embolism" and "Thrombosis" OR "Intracranial Hemorrhage"	67,722 .
S3		(MH "Stroke") OR (TI "Stroke") OR (AB "Stroke")	82,185
S4		(MH "Cardiovascular Disease") OR (TI "Cardiovascular Disease") OR (AB "Cardiovascular Disease") OR (TI "Vascular Diseases") OR (AB "Vascular Diseases")	31,156
S5		("Cerebrovascular Disease+") Here the subject heading has been explored to contain narrower and more explicit terms including ("Vascular Diseases") OR ("Aneurysm") OR ("Angioedema") OR ("Angiomatosis") OR "(Aortic Diseases") OR ("Arterial Dissections") OR ("Arterial Occlusive Diseases") OR ("Arteritis") OR ("Capillary Leak Syndrome")	2,808
S6		(MH "Vascular Headache") OR (TI "Vascular Headache") OR (AB "Vascular Headache") OR (TI "Vasculitis, Central Nervous System") OR (AB "Vasculitis, Central Nervous System") OR (MH "Vertebral Artery Dissections") OR (AB ""Vertebral Artery Dissections")	596
S7	Population B Traumatic Brain Injury	(MH "Brain injur*") OR (TI "Brain injur*") OR (AB ""Brain injur*") OR (MH "Hypoxia-Ischemia, Brain") OR (TI "Hypoxia-Ischemia, Brain") OR (AB ""Hypoxia-Ischemia, Brain")	21,774

S8	Population C Hypoxia	(MH "Hypoxia, Brain") OR (TI "Hypoxia, Brain") OR (AB "Hypoxia, Brain") OR (TI "Hypoxia-Ischemia, Brain") OR (AB "Hypoxia-Ischemia, Brain") OR (TI "Altered Cerebral Tissue Perfusion ('NANDA')") OR (AB "Altered Cerebral Tissue Perfusion ('NANDA')")	415
S9	Population D Infection	(MH "Purpura, Schoenlein-Henoch") OR (AB "Purpura, Schoenlein-Henoch") OR (MH "Vasculitis, Central Nervous System")	No results were found.
S10		(TI "Subacute Sclerosing Panencephalitis") OR (AB"Subacute Sclerosing Panencephalitis")	107
S11	Population E Toxic/Metabolic	(MH" Arsenic Poisoning") OR (MH "Street Drugs")	4,074
S12		(TI "Alcohol poising") (AB "Alcohol poising") OR (AB "Alcohol Withdrawal Seizures") OR (AB "Alcohol Withdrawal Delirium")	21
S13	Population F Prolonged disorder of consciousness terminology	(MM "Neurobehavioral Manifestations+") OR ("Catatonia") OR ("Communicative Disorders") OR ("Confusion")	58,297
S14		(MH "Consciousness Disorders")	584
S15		(MH "Coma") OR (AB "Coma") OR (TI "Coma") (AB "Unconsciousness") OR (TI "Unconsciousness")	6,196
S16		(MH "Carotid Sinus Syndrome") OR (AB "Syncope, Vasovagal") OR (TI "Syncope, Vasovagal")	53
S17		(TI "Vegetative state*") OR (AB "Vegetative state*") OR (TI "Persistent Vegetative State") OR (AB "Persistent Vegetative State")	701

S18		(MH “Minimally conscious state*”) OR (AB “Minimally conscious state*”) OR (TI “Minimally conscious state*”)	485
S19	Intervention 1 Standing devices	(MH “Tilt table”)	No results were found.
S20		(TI "Tilt table")	127
S21		(AB "Tilt table")	250
S22		(MH “ERIGO”)	No results were found.
S23		(TI “ERIGO”)	No results were found.
S24		(AB "stand aid")	3
S25		(TI "stand aid")	No results were found.
S26		(TI "Oswestry standing frame")	2
S27		(AB "Oswestry standing frame")	3

S28		(TX "Oswestry standing frame")	5
S29		(MH "standing frame")	No results were found.
S30		(TI "standing frame")	11
S31		(AB "standing frame")	37
S32	Intervention 2 stand	(TI "sit to stand") OR (AB "sit to stand")	1,016
S33		(MH "sitting balance")	No results were found.
S34		(TI "sitting balance")	37
S35		(AB "sitting balance")	126
S36		(TI "balance")	10,776
S37		(AB "balance")	28,106

S38		(MH "Balance, Postural")	11,872
S39		(MH “Stand*”) OR (TI “Stand*”) OR (AB “Stand*”)	239,765
S40		(MH “Rise*”) OR (TI “Rise*”) OR (AB “Rise*”)	25,240
S41		(MH “Assisted stand”) OR (TI “Assisted stand”) OR (AB “Assisted stand”)	1
S42		(TI “Lifting and Transfer Equipment”) OR (AB “Lifting and Transfer Equipment”)	No results were found.
S43		(TI “Hoists”) OR (AB “Hoists”)	77
S44		(TI “Patient Transfer Board”) OR (AB “Patient Transfer Board”)	2
S45	Intervention 3 Rehabilitation	(MH “Rehabilitation”) OR (TI “Rehabilitation”) OR (AB “Rehabilitation”) OR (TI “Rehab”) OR (AB “Rehab) OR (TI “Rehabilitation nurses”) OR (AB “Rehabilitation nurses”)	76,992
S46		(mt) "Physiotherapy" Here the subject heading has been explored to contain narrower and more explicit terms including (“The Chartered Society of Physiotherapy”) OR (“Australian Physiotherapy Association”) OR (“Students, Physical Therapy”) OR (“Physical Therapy Practice, Research-Based”) OR (“Physiotherapy Evidence Database OR Canadian Physiotherapy Association”) OR (“Physical Therapy Practice, Evidence-Based”) OR (“Physical Therapy OR The Chartered Society of Physiotherapy OR Students, Physical Therapy”)	21

S47	Outcome	(TI “Coma Recovery Scale Revised”) OR (AB “Coma Recovery Scale Revised”) OR (TI “CRS-R”) OR (AB “CRS-R”) OR (TI “Glasgow coma scale”) OR (AB “Glasgow coma scale”) (TI “GCS”) OR (AB “GCS”) OR (TI “Wessex Head Injury Matrix”) OR (AB “Wessex Head Injury Matrix”) OR (TI “WHIM”) OR (AB “WHIM”) OR (TI “Sensory Modality Assessment and Rehabilitation Technique”) OR (AB “Sensory Modality Assessment and Rehabilitation Technique”) OR (TI “SMART”) OR (AB “SMART”) OR (TI “Sensory Tool to assess responsiveness”) OR (AB “Sensory Tool to assess responsiveness”) OR (TI “STAR”) OR (AB “STAR”) OR (TI “Neurobehavioral tool”) OR (AB “Neurobehavioral tool”)	10,287
S48		(MH “Level of consciousness”) OR “Consciousness Disorders” OR “Arousal” OR “Wakefulness” OR (MH “Alertness”)	241
S49	Population	(S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28)	223,928
S50	Intervention 1	(S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42)	352
S51	Intervention 2	(S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54 OR S55 OR S56)	297,283
S52	Intervention 3	(S58 OR S59)	77,010
S53	Outcome	(S61 OR S62)	10,526
S54	P I1 O	S29 AND S43 AND S63	No results were found.

S55	P I2 O	S29 AND S57 AND S63	242
S56	P I3 O	S29 AND S60 AND S63	196

No studies were found that met inclusion criteria.

Medline 25/2/18

Number	PICO	Search term and Field	Hits
S1	Population A Aetiology Vascular event	(MH "Stroke") OR (AB "Stroke") OR (TI Stroke") OR (MH "Stroke, Lacunar") OR (AB "Stroke, Lacunar") OR (TI "Stroke, Lacunar") OR (MH "Stroke Rehabilitation") OR (AB "Stroke Rehabilitation") OR (TI "Stroke Rehabilitation") OR (TI "National Institute of Neurological Disorders and Stroke") OR (AB "National Institute of Neurological Disorders and Stroke")	200,994
S2	Population B Traumatic Brain Injury/ Brain injury*	(MH "Brain Injury, Chronic") OR (TI "Brain Injury, Chronic") OR (AB"Brain Injury, Chronic") OR (MH "Brain Injuries") OR (TI "Brain Injuries") OR (AB "Brain Injuries") OR (MH "Brain Injuries, Traumatic") OR (TI "Brain Injuries, Traumatic") OR (AB "Brain Injuries, Traumatic") OR (MH "Brain Injuries, Diffuse") OR (TI "Brain Injuries, Diffuse") OR (AB "Brain Injuries, Diffuse") OR (MH "Cerebrovascular Trauma") OR (TI "Cerebrovascular Trauma") OR (AB "Cerebrovascular Trauma") OR (MH "Head Injuries, Penetrating") OR (TI "Head Injuries, Penetrating") OR (AB "Head Injuries, Penetrating") OR (MH "Brain Concussion") OR (TI "Brain Concussion") OR (AB "Brain Concussion") OR (MH "Cerebrovascular Trauma") OR (TI "Cerebrovascular Trauma") OR (AB "Cerebrovascular Trauma") OR (MH "Head Injuries, Penetrating") OR (TI "Head Injuries, Penetrating") OR (AB ""Head Injuries, Penetrating")	60,537
S3	Population C Hypoxia	(MH "Hypoxia, Brain") OR (TI "Hypoxia, Brain") OR (AB "Hypoxia, Brain") OR (MH "Hypoxia-Ischemia, Brain") OR (TI "Hypoxia-Ischemia, Brain") OR (AB "Hypoxia-Ischemia, Brain")	11,754
S4	Population D Infection	(MH "Vasculitis") OR (TI "Vasculitis") OR (AB "Vasculitis") OR (TI "Vasculitis, Central Nervous System") OR (AB "Vasculitis, Central Nervous System")	32,538

S5		(MH “Encephalitis”) OR (TI “Encephalitis”) OR (AB “Encephalitis”) (TI “Anti-N-Methyl-D-Aspartate Receptor Encephalitis”) OR (AB “Anti-N-Methyl-D-Aspartate Receptor Encephalitis “Cerebral Ventriculitis”) OR (TI “Infectious Encephalitis”) OR (AB “Infectious Encephalitis”) OR (TI “Encephalitis, Viral”) OR (AB “Encephalitis, Viral”) (TI “Limbic Encephalitis”) OR (AB “Limbic Encephalitis”)	31,083
S6	Population F Prolonged disorder of consciousness terminology	(MH “Consciousness Disorders”) OR (TI “Consciousness Disorders”) OR (AB “Consciousness Disorders”) OR (TI “Consciousness”) OR (AB “Consciousness”)	31,857
S7		(MH “Vegetative state”) OR (TI “Vegetative state”) OR (AB “Vegetative state”) OR (MH “Persistent Vegetative State”) OR (TI “Persistent Vegetative State”) OR (AB “Persistent Vegetative State”) OR (MH “Coma, Post-Head Injury”) OR (TI “Coma, Post-Head Injury”) OR (AB “Coma, Post-Head Injury”) OR (MH “Minimally conscious state*”) OR (TI “Minimally conscious state*”) OR (AB “Minimally conscious state*”)	4,651
S8	Intervention 1 Standing devices	(MH “Tilt table”) OR (TI “Tilt table”) OR (AB “Tilt table”) OR (MH “ERIGO”) OR (TI “ERIGO”) OR (AB “ERIGO”)	1,225
S9	Intervention 2 Stand	(MH "stand aid") OR (TI "stand aid") OR (AB "stand aid")	No results were found.
S10		(TI "Oswestry standing frame")	1
S11		(AB "Oswestry standing frame")	3
S12		(TI "standing frame") OR (AB "standing frame")	59
S13		(TI "sit to stand") OR (AB "sit to stand")	1,699
S14		(TI "sitting balance") OR (AB "sitting balance")	257
S15		(TI "standing frame")	12
S16		(AB "standing frame")	53
S17		(MH “Rise*”) OR (TI “Rise*”) OR (AB “Rise*”)	242,951
S18		(MH “Posture”) OR (TI “Posture”) OR (AB “Posture”)	74,052
S19	Intervention 3 Rehabilitation	(“Rehabilitation”+) OR (TI “Stroke Rehabilitation”) OR (AB “Stroke Rehabilitation”) OR (TI “Rehabilitation Research”) OR (AB “Rehabilitation Research”) OR (TI “Physical and Rehabilitation Medicine”) OR (AB “Physical and Rehabilitation Medicine”) OR (TI “Neurological Rehabilitation”) OR (AB “Neurological Rehabilitation”) OR (TI “Rehabilitation Nursing”) OR (AB “Rehabilitation Nursing”) OR (TI “Rehabilitation Centers”) OR (AB “Rehabilitation Centers”)	361,019

S20		(MH “Physiotherapy”) OR (TI “Physiotherapy”) OR (AB “Physiotherapy”) OR (TI “Physical Therapy Modalities”) OR (AB “Physical Therapy Modalities”) OR (TI “Physical Therapy Specialty”) OR (AB “Physical Therapy Specialty”)	15,675
S21		(MH “Occupational Therapy”) OR (TI ““Occupational Therapy”) OR (AB “Occupational Therapy”) OR (MH “Occupational Therapy Department, Hospital”) OR (TI “Occupational Therapy Department, Hospital”) OR (AB “Occupational Therapy Department, Hospital”)	11,994
S22	Outcome	(MH “Level of consciousness”) OR (TI “Level of consciousness”) OR (AB “Level of consciousness”)	3,262
S23		(MH “Consciousness disorder”) OR (TI “Consciousness disorder”) OR (AB “Consciousness disorder”)	127
S24		(MH “Alertness”) OR (TI “Alertness”) OR (AB “Alertness”)	5,703
S25		(TI “Coma Recovery Scale Revised”) OR (AB “Coma Recovery Scale Revised”) OR (TI “CRS-R”) OR (AB “CRS-R”) OR (TI “Glasgow coma scale”) OR (AB “Glasgow coma scale”) (TI “GCS”) OR (AB “GCS”) OR (TI “Wessex Head Injury Matrix”) OR (AB “Wessex Head Injury Matrix”) OR (TI “WHIM”) OR (AB “WHIM”) OR (TI “Sensory Modality Assessment and Rehabilitation Technique”) OR (AB “Sensory Modality Assessment and Rehabilitation Technique”) OR (TI “SMART”) OR (AB “SMART”) OR (TI “Sensory Tool to assess responsiveness”) OR (AB “Sensory Tool to assess responsiveness”) OR (TI “STAR”) OR (AB “STAR”) OR (TI “Neurobehavioral tool”) OR (AB “Neurobehavioral tool”)	41,354
S26	Population	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7	362,080
S27	Intervention 1	S8	1,225
S28	Intervention 2	S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18	318,274
S29	Intervention 3	S19 OR S20 OR S21	377,375
S30	Outcome	S22 OR S23 OR S24 OR S25	50,148
S31	Combination 1	S26 AND S27 AND S30 Population AND Intervention 1 (tilt table synonyms) AND Outcome	5
S32	Combination 2	S26 AND S28 AND S3 Population AND Intervention 2 standing devices AND outcome	86
S33	Combination 3	S26 AND S29 AND S30 Population AND Intervention 3 Rehabilitation synonyms outcome AND outcome	678
S34		S26 AND S25 AND S30 Population AND Intervention 3 Rehabilitation synonyms AND neurobehavioral scale synonyms	495

Three papers retrieved through Medline database search

A) Frazzitta, G., Zivi, I., Valsecchi, R., Bonini, S., Maffia, S., Molatore, K., Sebastianelli, L., Zarucchi, A., Matteri, D., Ercoli, G., Maestri, R., and Saltuari, L. (2016) 'Effectiveness of a very Early Stepping Verticalization Protocol in Severe Acquired Brain Injured Patients: A Randomized Pilot Study in Icu'. *PLoS ONE* 11 (7), 1-15
B) Bartolo, M., Bargellesi, S., Castioni, C. A., Bonaiuti, D., Antenucci, R., Benedetti, A., Capuzzo, V., Gamna, F., Radeschi, G., Citerio, G., Colombo, C., Del Casale, L., Recubini, E., Toska, S., Zanello, M., D'Aurizio, C., Spina, T., Del Gaudio, A., Di Rienzo, F., Intiso, D., Dallocchio, G., Felisatti, G., Lavezzi, S., Zoppellari, R., Gariboldi, V., Lorini, L., Melizza, G., Molinero, G., Mandal, G., Pignataro, A., Montis, A., Napoleone, A., Pilia, F., Pisu, M., Semerjian, M., Pagliaro, G., Nardin, L., Scarponi, F., Zampolini, M., Zava, R., Massetti, M. A., Piccolini, C., Aloj, F., Antonelli, S., and Zucchella, C. (2016) 'Early Rehabilitation for Severe Acquired Brain Injury in Intensive Care Unit: Multicenter Observational Study'. *European Journal of Physical and Rehabilitation Medicine* 52 (1), 90-100
C) Krewer, C., Luther, M., Koenig, E., and Muller, F. (2015) 'Tilt Table Therapies for Patients with Severe Disorders of Consciousness: A Randomized, Controlled Trial'. *PloS One* 10 (12), 1-14

The above search strategies were also run in these databases: -

AMED	No relevant results retried.
PEDro	No relevant results retried.
The Cochrane library	No relevant results retried.
SCOPUS	No relevant results retried.

Appendix 1.3 Post citation searching of key author in Scopus

Paper title	Articles that have cited this paper	Articles that have cited this paper that are suitable for inclusion	Main author	Number of articles authored by key author	Articles authored by key author for inclusion
'Effectiveness of a very Early Stepping Verticalization Protocol in Severe Acquired Brain Injured Patients: A Randomized Pilot Study in Icu Frazzitta et al. (2016)	Early verticalization in patients in a vegetative or minimally conscious state Frazzitta, G._, Zivi, I. , Valsecchi, R. *(2018) Biosystems and Biorobotics* Book chapter Randomization Test: An Alternative Analysis for the Difference of Two Means Nuzzo, R.L. *(2017)*	None	Frazzitta, Giuseppe	63	None other than the searched for study.
Early Rehabilitation for Severe Acquired Brain Injury in Intensive Care Unit: Multicenter Observational Study. European Journal of Physical and Rehabilitation Medicine 52 (1), 90-100 Bartolo et al. (2016)	Zero	None	Bartolo, Michelangelo	8	None
Tilt table therapies for patients with severe disorders of consciousness: A randomized, controlled trial Krewer et al. (2015)	Early verticalization in patients in a vegetative or minimally conscious state (Book Chapter) Frazzitta, G. Zivi, I. Valsecchi, R. Saltuari, L. Spasticity management in disorders of consciousness Effectiveness of a very early stepping verticalization protocol in severe acquired brain injured patients: A randomized pilot study in icu. Frazzitta et al. (2016)	None	Krewer, Carmen	26	Luther, M.S., Krewer, C., Müller, F., Koenig, E. Comparison of orthostatic reactions of patients still unconscious within the first three months of brain injury on a tilt table with and without integrated stepping. A prospective, randomized crossover pilot trial (2008) *Clinical Rehabilitation*, 22 (12), pp. 1034-1041.

	The role of the psychologist with disorders of consciousness in inpatient pediatric neurorehabilitation: A case series (Article) Lahey, S. Beaulieu, C., Sandbach, K., Colaiezzi, A., Balkan, S. People with disorders of consciousness Annen, J., Laureys, S., Gosseries, O. Severe disorders of consciousness in early neurological and neurosurgical rehabilitation(Article) Bender, A. (2016) "Schwere Bewusstseinsstörungen in der neurologisch-neurochirurgischen Frührehabilitation"				

Appendix 1.4 Articles found through searching reference list of included articles

Paper title	Articles for inclusion from reference list
Frazzitta, G., Zivi, I., Valsecchi, R., Bonini, S., Maffia, S., Molatore, K., Sebastianelli, L., Zarucchi, A., Matteri, D., Ercoli, G., Maestri, R., and Saltuari, L. (2016) 'Effectiveness of a very Early Stepping Verticalization Protocol in Severe Acquired Brain Injured Patients: A Randomized Pilot Study in Icu'. PLoS ONE 11 (7) 37 references	Elliott, L., Coleman, M., Shiel, A., Wilson, B.A., Badwan, D., Menon, D., Pickard, J. Effect of posture on levels of arousal and awareness in vegetative and minimally conscious state patients: A preliminary investigation (2005) *Journal of Neurology, Neurosurgery and Psychiatry*, 76 (2), pp. 298-299 Toccolini, B. F., RT, Osaku, Erica Fernanda, RT, MSc, de Macedo Costa, Claudia Rejane Lima, RT, MSc, Teixeira, S. N., RT, Costa, N. L., RT, Cândia, M. F., RT, Leite, M. A., RT, de Albuquerque, Carlos Eduardo, RT, MSc, Jorge, Amaury Cezar, MD, MSc, and Duarte, Péricles Almeida Delfino, MD, PhD (2015) 'Passive Orthostatism (Tilt Table) in Critical Patients: Clinicophysiologic Evaluation'. Journal of Critical Care 30 (3) Krewer, C., Luther, M., Koenig, E., and Muller, F. (2015) 'Tilt Table Therapies for Patients with Severe Disorders of Consciousness: A Randomized, Controlled Trial'. *PloS One* 10 (12), 1-14 Luther, M.S., Krewer, C., Müller, F., Koenig, E. Comparison of orthostatic reactions of patients still unconscious within the first three months of brain injury on a tilt table with and without integrated stepping. A prospective, randomized crossover pilot trial (2008) *Clinical Rehabilitation*, 22 (12), pp. 1034-1041.

Bartolo, M., Bargellesi, S., Castioni, C. A., Bonaiuti, D., Antenucci, R., Benedetti, A., Capuzzo, V., Gamna, F., Radeschi, G., Citerio, G., Colombo, C., Del Casale, L., Recubini, E., Toska, S., Zanello, M., D'Aurizio, C., Spina, T., Del Gaudio, A., Di Rienzo, F., Intiso, D., Dallocchio, G., Felisatti, G., Lavezzi, S., Zoppellari, R., Gariboldi, V., Lorini, L., Melizza, G., Molinero, G., Mandal, G., Pignataro, A., Montis, A., Napoleone, A., Pilia, F., Pisu, M., Semerjian, M., Pagliaro, G., Nardin, L., Scarponi, F., Zampolini, M., Zava, R., Massetti, M. A., Piccolini, C., Aloj, F., Antonelli, S., and Zucchella, C. (2016) 'Early Rehabilitation for Severe Acquired Brain Injury in Intensive Care Unit: Multicenter Observational Study'. European Journal of Physical and Rehabilitation Medicine 52 (1), 90-100 40 references	None relevant to inclusion criteria
Krewer, C., Luther, M., Koenig, E., and Muller, F. (2015) 'Tilt Table Therapies for Patients with Severe Disorders of Consciousness: A Randomized, Controlled Trial'. PloS One 10 (12) 34 references	Elliott, L., Coleman, M., Shiel, A., Wilson, B.A., Badwan, D., Menon, D., Pickard, J. Effect of posture on levels of arousal and awareness in vegetative and minimally conscious state patients: A preliminary investigation (2005) *Journal of Neurology, Neurosurgery and Psychiatry*, 76 (2), pp. 298-299 Wilson, B.A., Dhamapurkar, S., Tunnard, C., Watson, P., Florschutz, G. The effect of positioning on the level of arousal and awareness in patients in the vegetative state or the minimally conscious state: A replication and extension of a previous finding (2013) *Brain Impairment*, 14 (3), pp. 475-479. http://journals.cambridge.org/action/displayBackIssues?jid=BIM Riberholt, C. G., Thorlund, J. B., Mehlsen, J., and Nordenbo, A. M. (2013) 'Patients with Severe Acquired Brain Injury show Increased Arousal in Tilt-Table Training'. *Danish Medical Journal* 60 (12), 1-8 Luther, M.S., Krewer, C., Müller, F., Koenig, E. Orthostatic circulatory disorders in early neurorehabilitation: A case report and management overview (2007) *Brain Injury*, 21 (7), pp. 763-767. Luther, M.S., Krewer, C., Müller, F., Koenig, E. Comparison of orthostatic reactions of patients still unconscious within the first three months of brain injury on a tilt table with and without integrated stepping. A prospective, randomized crossover pilot trial (2008) *Clinical Rehabilitation*, 22 (12), pp. 1034-1041.

Appendix 1.5 Narrowly excluded articles

Title of paper	Reason for exclusion
Klein, K., Mulkey, M., Bena, J.F., Albert, N.M. Clinical and psychological effects of early mobilization in patients treated in a neurologic ICU: A comparative study (2015) Critical Care Medicine, 43 (4), 865-873.	No evaluation of consciousness
Luther, M. S., Krewer, C., Müller, F., and Koenig, E. (2007) 'Orthostatic Circulatory Disorders in Early Neurorehabilitation: A Case Report and Management Overview'. *Brain Injury* 21 (7), 763-767	No evaluation of consciousness
Kuznetsov, A. N., Rybalko, N. V., Daminov, V. D., and Luft, A. R. (2013) 'Early Poststroke Rehabilitation using a Robotic Tilt-Table Stepper and Functional Electrical Stimulation'. *Stroke Research and Treatment*, 1-9	No evaluation of consciousness.
Luther, M. S., Krewer, C., Müller, F., and Koenig, E. (2007) 'Orthostatic Circulatory Disorders in Early Neurorehabilitation: A Case Report and Management Overview'. *Brain Injury* 21 (7), 763-767	No evaluation of consciousness.
Sibinelli, M., Maioral, D., Cristina, F., Antônio L. E., Kosour, C., Dragosavac, D., & Lima, N. M. F. V., (2012). The effects of orthostatism in adult intensive care unit patients. *Revista Brasileira de Terapia Intensiva*, *24*(1), 64-70 [online] available from <https://dx.doi.org/10.1590/S0103-507X2012000100010> [12/2/18]	No categorisation of consciousness.

Appendix 1.6 Cochrane data collection form

Data collection form for *A systematised review of assisted standing for persons in a prolonged disorder of consciousness*

Data collection form for intervention reviews: RCTs and non-RCTs amended from Cochrane Group

Version 3, April 2014

Removed for archiving please refer to - Higgins, J. P. T. and Green, S. (2011) 'Version 5.1.0 (Updated March 2011)'. in *Cochrane Handbook for Systematic Reviews of Interventions*. Oxford: The Cochrane Collaboration [online] available from <http://training.cochrane.org/handbook> [10/10/17]

1.7 Downs and Black (1998)

Removed for archiving please refer to - Downs, S. H. and Black, N. (1998) 'The Feasibility of Creating a Checklist for the Assessment of the Methodological Quality both of Randomised and Non-Randomised Studies of Health Care Interventions'. *Journal of Epidemiology and Community Health* 52 (6), 377-384

Appendix 1.8 Original results provided by the studies

Bartolo et al. (2016) (GCS minimum score 3 – maximum score 15)

Time	GCS score non-mobilisation	GCS score mobilisation
1st evaluation (baseline)	5.7 (4.7–6.9)	7.3 (6.4–8.3)
2nd evaluation	7.0 (5.8–8.5)	8.7 (7.7–9.9)
3rd evaluation	7.1 (5.8–8.8)	9.2 (8.1–10.5)
4th evaluation	6.9 (5.5–8.8)	9.8 (8.5–11.2)
At discharge	7.3 (6.1–8.7)	10.3 (9.2–11.6)

Elliott et al. (2005) (WHIM minimum score 0 – maximum score 62)

Number	Level of consciousness	Supine score	Standing score
1	VS	43	43
2	VS	4	4
3	VS	5	26
4	VS	1	49
5	VS	14	26
6	MCS	13	16

7	MCS	20	36
8	MCS	26	34
9	MCS	14	14
10	MCS	18	28
11	MCS	8	23
12	MCS	42	43

Frazzitta et al. (2016) (CRS-R minimum score 0 – maximum score 23)

Time	Early vertiicalisation (CRS-R)	Controls (CRS-R)
Admission	4.0 (3.0, 5.7)	5.0 (3.0, 12.0)
ICU discharge	19.0 (5.0, 20.8)	10.5 (3.3, 18.0)
Neurorehabilitation Discharge	23.0 (9.4, 23.0)	13.0 (7.0, 23.0)

Greco et al. (2013)

Median and median absolute deviation of Power Spectral Density (PSD) for each bandwidth and region reported in a logarithmic scale. No minimal and maximal scores verified.

Patient	Region	δ		θ		α		β	
		0 degrees	60 degrees	0 degrees	60 degrees	0 degrees	60 degrees	0 degrees	60 degrees
1	Left	2.16 ± 0.19	2.14 ± 0.11	1.53 ± 0.17	1.64 ± 0.11	0.42 ± 0.09	1.14 ± 0.08	1.34 ± 0.15	2.19 ± 0.13
	Right	2.40 ± 0.21	2.62 ± 1.94	1.77 ± 0.11	1.85 ± 0.11	0.97 ± 0.15	1.46 ± 0.05	1.91 ± 0.12	2.42 ± 0.12
2	Left	1.91 ± 0.1	3.34 ± 0.1	1.82 ± 0.1	2.23 ± 0.08	1.28 ± 0.27	1.83 ± 0.05	0.35 ± 0.06	1.81 ± 0.14
	Right	1.4 ± 0.11	2.48 ± 0.18	1.5 ± 0.15	1.69 ± 0.1	1.46 ± 0.19	2.04 ± 0.13	1.07 ± 0.1	2.01 ± 0.06
3	Left	1.34 ± 0.12	1.72 ± 0.1	0.9 ± 0.08	1.2 ± 0.07	0.59 ± 0.15	0.71 ± 0.07	-0.19 ± 0.15	0.59 ± 0.01
	Right	1.61 ± 0.08	2.16 ± 0.17	1.39 ± .14	1.7 ± 0.07	0.54 ± 0.20	0.93 ± 0.05	-0.28 ± 0.14	0.56 ± 0.03

Median and median absolute deviation of Brain Symmetry Index for each bandwidth and region reported in a logarithmic scale

Patient	δ		θ		α		β	
	0 degrees	60 degrees	0 degrees	60 degrees	0 degrees	60 degrees	0 degrees	60 degrees
1	0.51 ± 0.03	0.49 ± 0.04	0.48 ± 0.02	0.47 ± 0.03	0.50 ± 0.002	0.49 ± 0.02	0.46 ± 0.007	0.43 ± 0.006
2	0.52 ± 0.02	0.53 ± 0.01	0.54 ± 0.01	0.55 ± 0.01	0.55 ± 0.02	0.54 ± 0.02	0.55 ± 0.008	0.46 ± 0.01
3	0.47 ± 0.02	0.48 ± 0.03	0.5 ± 0.01	0.51± 0.02	0.39 ± 0.01	0.41 ± 0.01	0.4 ± 0.007	0.36 ± 0.008

Krewer et al. (2015) (CRS-R minimum score 0 – maximum score 23)

Patient	**Intervention**	**Baseline**	**Week 3**	**Week 6**
1	Erigo	6	6	8
2	Erigo	17	20	23
4	TT	12	16	21
5	TT	7	15	19
6	TT	13	23	23
7	Erigo	14	16	17
8	Erigo	13	4	4*
9	Erigo	7	14	18
10	TT	3	8	8*
12	TT	9	15	16
13	TT	8	9	11
14	TT	13	17	21
16	Erigo	13	12	12*
17	Erigo	10	16	13
18	Erigo	14	18	18
19	TT	10	21	19
20	TT	13	22	23
21	Erigo	7	10	6
22	Erigo	15	6	6*
23	Erigo	11	23	23

25	TT	15	19	17
26	TT	14	23	23
27	Erigo	10	10	8
28	TT	14	17	19
29	TT	12	20	23
30	Erigo	10	12	17
31	TT	11	19	20
32	Erigo	10	19	22
33	TT	12	10	10*
34	Erigo	5	8	11
36	Erigo	13	14	18
37	TT	15	18	22
38	TT	15	19	23
39	TT	15	23	23
40	Erigo	8	12	12
41	Erigo	18	16	16*
42	Erigo	14	19	21
43	TT	9	12	19
44	Erigo	12	12	9
45	TT	9	13	19
46	Erigo	16	21	20
47	TT	8	9	17
49	TT	7	9	6
50	Erigo	12	13	13

Luther et al. (2008) (CRS-R minimum score 0 – maximum score 23) – data only presented narratively as below

A comparison of the CRS-R before and after treatment showed similar behaviour on both devices. Two patients improved (by one and two items on the tilt table plus stepping versus one and three items on the normal tilt table) and one experienced a decrease (four items on the tilt table plus stepping and one item on the conventional tilt table, respectively) of the CRS-R score. Six patients did not show any change.

Taveggia et al. (2015) (CRS-R minimum score 0 – maximum score 23; LCF minimum score 1 – maximum score 8) – data only presented narratively as below

A comparison of CRS and LCF before and after treatment showed no change in both groups.

Toccolini et al. (2015) (GCS minimum score 3 – maximum score 15)

	GCS 1st day			GCS 2nd day					GCS last day				
	30°	**40°**	**30°**	**45°**	**60°**	**75°**	**90°**	**60°**	**30°**	**45°**	**60°**	**75°**	**90°**
Group average	~5.5	~5.6	~6.2	~6.3	~6.3	~6.5	~6.9	~7.4	~8.1	~7.9	~8.1	~8.2	~8.6

Riberholt et al. (2013)

Amount of time with eyes open pre-intervention	% of time pre-intervention	Amount of time with eyes open during intervention	% of time during intervention
7 minutes	22.1%	9.5 minutes	66%

Wilson et al. (2013) (WHIM minimum score 0 – maximum score 62)

	Sitting versus supine (%)	Standing versus supine (%)	Standing versus sitting (%)
VS patients (n = 8)	50	75	50
MCS patients (n = 8)	75	75	87.5
Total (n = 16)	62.50	75	68.75